364

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PASSWORD:
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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

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NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
NEWS  3  Jun 03  New e-mail delivery for search results now available
NEWS  4  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
NEWS  5  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
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                 ENERGY, INSPEC
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NEWS 25  Feb 26  PCTFULL now contains images
NEWS 26  Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27  Mar 20  EVENTLINE will be removed from STN
NEWS 28  Mar 24  PATDPAFULL now available on STN
NEWS 29  Mar 24  Additional information for trade-named substances without
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NEWS 34  Apr 21  New current-awareness alert (SDI) frequency in
                 WPIDS/WPINDEX/WPIX
NEWS 35  Apr 28  RDISCLOSURE now available on STN
NEWS 36  May 05  Pharmacokinetic information and systematic chemical names
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NEWS 37  May 15  MEDLINE file segment of TOXCENTER reloaded
NEWS 38  May 15  Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39  May 16  CHEMREACT will be removed from STN
NEWS 40  May 19  Simultaneous left and right truncation added to WSCA
```

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NEWS 41   May 19  RAPRA enhanced with new search field, simultaneous left and
                  right truncation

NEWS EXPRESS   April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS     STN Operating Hours Plus Help Desk Availability
NEWS INTER     General Internet Information
NEWS LOGIN     Welcome Banner and News Items
NEWS PHONE     Direct Dial and Telecommunication Network Access to STN
NEWS WWW       CAS World Wide Web Site (general information)

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  * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:22:35 ON 21 MAY 2003

=> FILE REG
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 09:22:47 ON 21 MAY 2003
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STRUCTURE FILE UPDATES:   20 MAY 2003  HIGHEST RN 518004-10-9
DICTIONARY FILE UPDATES:  20 MAY 2003  HIGHEST RN 518004-10-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09849400.3

L1       STRUCTURE UPLOADED
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=> d l1
L1 HAS NO ANSWERS
L1                STR
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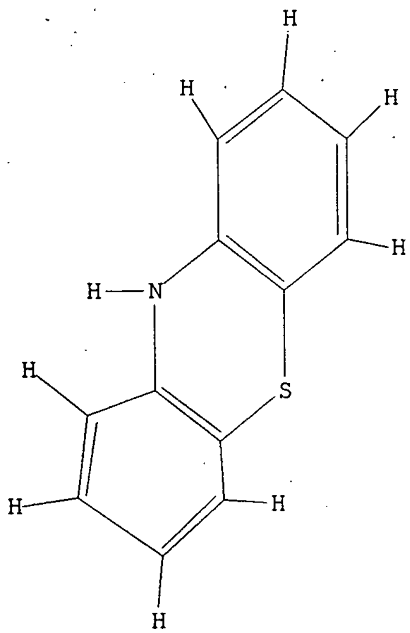

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Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 09:23:13 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   1631 TO ITERATE

 61.3% PROCESSED    1000 ITERATIONS                               10 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:        30198 TO    35042
PROJECTED ANSWERS:              84 TO      568

L2            10 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 09:23:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  31556 TO ITERATE

100.0% PROCESSED   31556 ITERATIONS                              376 ANSWERS
SEARCH TIME: 00.00.01

L3           376 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
```

364

Welcome to STN International! Enter x:x

LOGINID:ssspta1611sxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

```
* * * * * * * * * *  Welcome to STN International  * * * * * * * * * *

 NEVS  1         Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Jun 03  New e-mail delivery for search results now available
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 NEWS 20  Feb 13  CANCERLIT is no longer being updated
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 NEWS 25  Feb 26  PCTFULL now contains images
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 NEWS 28  Mar 24  PATDPAFULL now available on STN
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 NEWS 34  Apr 21  New current-awareness alert (SDI) frequency in
                  WPIDS/WPINDEX/WPIX
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 NEWS 38  May 15  Supporter information for ENCOMPPAT and ENCOMPLIT updated
 NEWS 39  May 16  CHEMREACT will be removed from STN
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 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:44:25 ON 21 MAY 2003

=> file reg
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                        0.21       0.21

FILE 'REGISTRY' ENTERED AT 08:44:33 ON 21 MAY 2003
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STRUCTURE FILE UPDATES:    20 MAY 2003  HIGHEST RN 518004-10-9
DICTIONARY FILE UPDATES:   20 MAY 2003  HIGHEST RN 518004-10-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09849400.2
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L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1                STR
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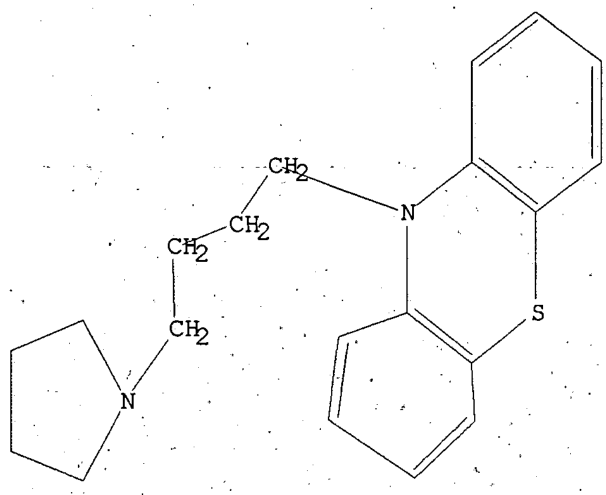

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Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 08:44:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      27 TO ITERATE

100.0% PROCESSED       27 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:          229 TO      851
PROJECTED ANSWERS:               0 TO        0

L2              0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 08:45:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    616 TO ITERATE

100.0% PROCESSED      616 ITERATIONS                             11 ANSWERS
SEARCH TIME: 00.00.01

L3             11 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       148.15     148.36

FILE 'CAPLUS' ENTERED AT 08:45:14 ON 21 MAY 2003
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FILE COVERS 1907 - 21 May 2003 VOL 138 ISS 21
FILE LAST UPDATED: 20 May 2003 (20030520/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

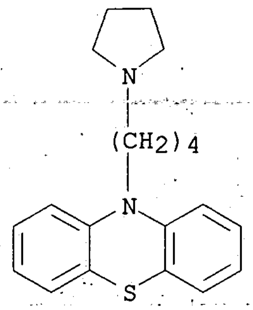
=> s l3
L4 20 L3

=> d l4 fbib hitstr abs total

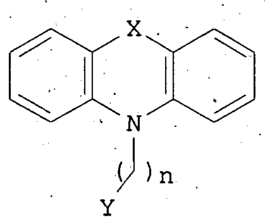
L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2003:118638 CAPLUS
DN 138:153540
TI Preparation of aminobutylphenothiazines, -iminodibenzyls, and related compounds as chemosensitizing agents against chloroquine resistant plasmodium falciparum
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003032801	A1	20030213	US 2001-849400	20010507
				US 2001-849400	20010507

OS MARPAT 138:153540
IT **443309-35-1P**, 10-(4-Pyrrolidin-1-ylbutyl)phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of aminobutylphenothiazines, -iminodibenzyls, and related compds. as chemosensitizing agents against chloroquine resistant plasmodium falciparum)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



GI



I

AB Title compds. [I; X = (substituted) alkyl, heteroatom; n = 4-6; Y = (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, NR1R2; R1, R2 = H, heteroatom, (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; each ring structure may be substituted], were prepd. Thus, 10-(4-pyrrolidin-1-ylbutyl)phenothiazine (general prepn. given) at 50 ng/mL completely restored the sensitivity of TM91C235 cells to chloroquine.

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:868744 CAPLUS
DN 137:370096
TI Tricyclic N-(aminoalkyl)-substituted phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines, active as chemosensitizing agents against chloroquine-resistant Plasmodium falciparum, and methods of making and using thereof
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA United States Army Medical Research and Material Command, USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002089810	A1	20021114	WO 2001-US14574	20010507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

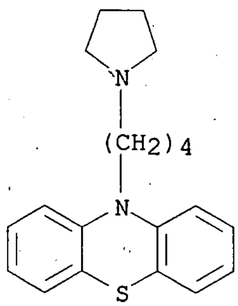
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
WO 2001-US14574 20010507

OS MARPAT 137:370096

IT **443309-35-1P**, 10-[4-(Pyrrolidin-1-yl)butyl]phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines as antimalarial sensitizing agents for treatment of multidrug-resistant malaria with chloroquine and mefloquine)

RN 443309-35-1 CAPLUS

CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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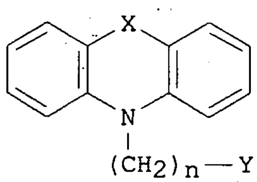
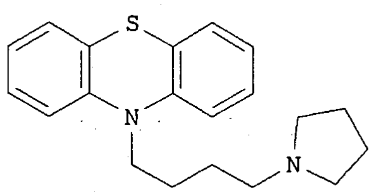


I



II

AB Title compds. I and pharmaceutically acceptable salts or prodrugs thereof are disclosed [wherein: X is a substituted or unsubstituted alkyl, a heteroatom, or 2 H atoms; n is 4, 5, or 6; Y is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or NR1R2; wherein R1 and R2 are each independently, H, a heteroatom, substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and wherein each ring structure is independently substituted or unsubstituted]. Also disclosed are chemosensitizing agents and methods of modulating, attenuating, reversing, or affecting a cell's or organism's resistance to a given drug such as an antimalarial. In particular, a group of compds. I were prepd. and shown to have improved anti-MDR (multidrug resistance) efficacy and reduced side effects (no data) in restoration of the clin. efficacy of antimalarials including mefloquine and chloroquine. Four of the compds. also showed moderate intrinsic

antimalarial activity in the absence of chloroquine or mefloquine. Structure-activity relationships, e.g., regarding alkyl chain length, ring rigidity, and amino terminal size, are discussed. For instance, 4-chloro-1-butanol was converted to the THP ether (99%) and then used to N-alkylate phenothiazine (46%), followed by deprotection (100%), conversion of the resultant alc. to a chloride with SOCl2 (62%), and amination of the chloride (34%) to give the pyrrolidine deriv. II. At 50 ng/mL in vitro, II completely restored the sensitivity of TM91C235 cells [a highly drug-resistant malaria isolate from Thailand] to chloroquine, giving 99% cell growth suppression/inhibition. When tested on a different clone of Plasmodium falciparum, II gave superior MDR-reversing activity, with a fractional inhibitory concn. (FIC) of 0.21, using a 1:1 combination of chloroquine and II.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 20 CAPLUS

AN 2002:372411 CAPLUS

DN 137:109247

TI Design, Synthesis, and Evaluation of New Chemosensitizers in Multi-Drug-Resistant Plasmodium falciparum

AU Guan, Jian; Kyle, Dennis E.; Gerena, Lucia; Zhang, Quan; Milhous, Wilbur K.; Lin, Ai J.

CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, MD, 20910, USA

SO Journal of Medicinal Chemistry (2002), 45(13), 2741-2748
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

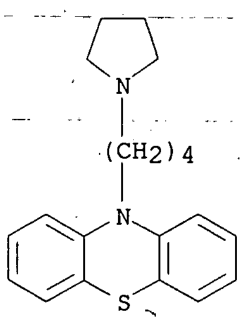
LA English

OS CASREACT 137:109247

IT **443309-35-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of antimalarial drug chemosensitizing aminoalkyl phenothiazines, benzazepines, and diphenylamines)

RN 443309-35-1 CAPLUS

CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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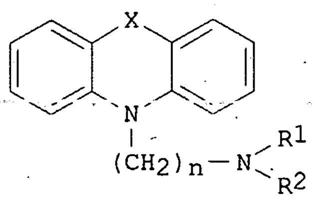
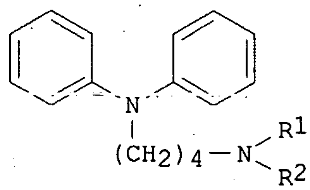

I

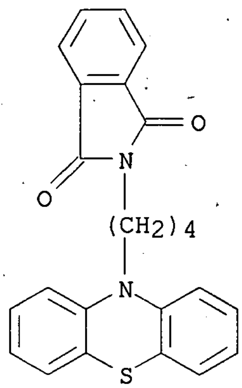

II

AB A series of new chemosensitizers (modulators) against chloroquine-resistant Plasmodium falciparum were designed and synthesized in an attempt to prep. modulators with enhancing drug-resistant reversing efficacy and minimal side effects. Phenothiazine, iminodibenzyl, and iminostilbene arom. amine ring systems I (X = S, CH2CH2, CH:CH; n = 4-6; R1, R2 = Me, Et, PhCH2; R1R2N = pyrrolinyl) and diphenylamines II (R1 = R2 = Et, R1R2N = pyrrolinyl) were examd. Various tertiary amino groups including either noncyclic or cyclic aliph. amines were introduced to explore the steric tolerance at the end of the side chain. The new compds. showed better drug-resistant reversing activity in chloroquine-resistant than in mefloquine-resistant cell lines and were generally more effective against chloroquine-resistant P. falciparum isolates from Southeast Asian (W2 and TM91C235) than those from South America (PC49 and RCS). Structure-activity relationship studies revealed that elongation of the alkyl side chain of the mol. retained the chemosensitizing activity, and analogs with four-carbon side chains showed superior activity. Furthermore, new modulators with phenothiazine ring exhibited the best chemosensitizing activity among the four different ring systems examd. Terminal amino function has limited steric tolerance as evidenced by the dramatic lose of the modulating activity, when the size of substituent at the amino group increases. The fractional inhibitory concn. (FIC) index of the best new modulator I (X = S, n = 4, R1R2N = pyrrolinyl) is 0.21, which is superior to that of verapamil (0.51), one of the best-known multi-drug-resistant reversing agents. Some of the analogs displayed moderate intrinsic in vitro antimalarial activity against a W-2 clone of P. falciparum.

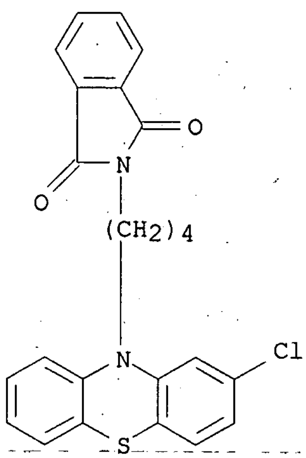
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD.
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:4293 CAPLUS
DN 132:273829
TI Relationship between cytotoxic activity and dipole moment for phthalimido- and chloroethyl-phenothiazines
AU Kurihara, Teruo; Motohashi, Noboru; Sakagami, Hiroshi; Molnar, Joseph
CS Faculty of Science, Josai University, Saitama, 350-0295, Japan
SO Anticancer Research (1999), 19(5B), 4081-4083
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(relationship between cytotoxic activity and dipole moment for phthalimido- and chloroethyl-phenothiazines)

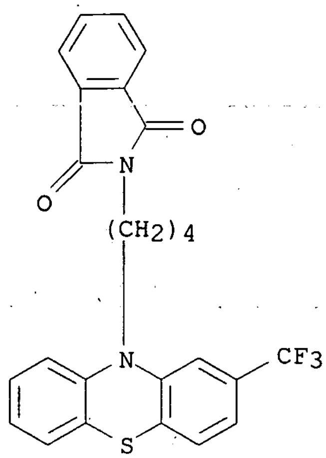
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



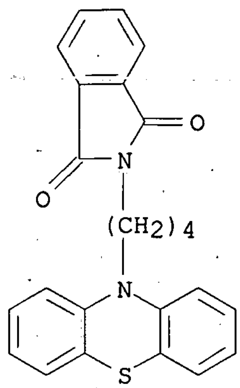
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



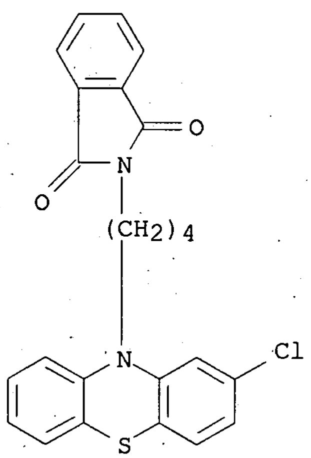
AB Among twelve phenothiazine-related compds., the cytotoxic activity of six "half-mustard type" phenothiazines was significantly higher than that of six phthalimido compds. 1-(2-Chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propylurea, 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butylurea and 1-(2-chloroethyl)-3-(2-trifluoromethyl-10H-phenothiazin-10-yl)butylurea showed the highest cytotoxic activity, in parallel with high .DELTA..mu. (difference between two dipole moments, .mu.g and .mu.e). There was also pos. relation between cytotoxic activity and MO energy such as .pi.-LUMO, .pi.-HOMO, and lone pair orbitals originated from O, N1, and N3 atoms. The present study demonstrated that cytotoxic activity of "half-mustard type" phenothiazines can be predicted by their dipole moments and MO energies.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

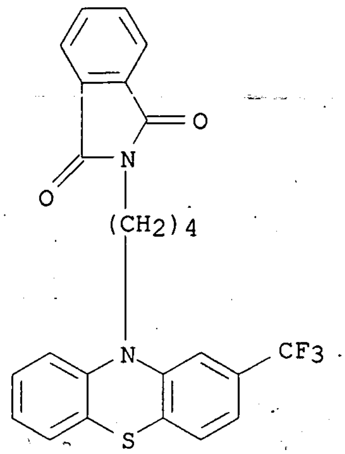
L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:654667 CAPLUS
DN 132:131770
TI Chemical structure and tumor type specificity of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Sakagami, Hiroshi; Szabo, Diana; Csuri, Klara; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji Pharmaceutical University, Tokyo, 204-8588, Japan
SO Anticancer Research (1999), 19(3A), 1859-1864
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chem. structure-activity and tumor-type specificity of half-mustard type phenothiazines)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



AB The antiproliferative activity of six half-mustard type phenothiazines against a total of 54 tumor cell lines: 4 leukemia, 9 non-small-cell lung, 7 colon-, 5 CNS-, 8 melanoma, 6 ovarian-, 8 renal-, 1 prostate and 6 breast cancer was detd. by NCI-Information Intensive-Approach. The C-2 position of phenothiazines were substituted with H, Cl and CF3 groups. The half-mustard and ring system was linked either by a propylene or a butylene bridge. Colon-cancer cell showed the highest sensitivity against half-mustard type phenothiazines, followed by leukemia, melanoma, prostate-, CNS-, breast-, lung-, renal and ovarian cancer cells. These data suggest the cancer-type-specific antitumor action of half-mustard type phenothiazines.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1998:282099 CAPLUS

DN 129:75984

TI The primary in vitro anticancer activity of "half-mustard type" phenothiazines in NCI's revised anticancer screening paradigm

AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Gupta, Radha Raman; Molnar, Joseph

CS Scriptgen Pharmaceuticals, Inc., Medford, MA, 02155, USA

SO Anticancer Research (1998), 18(1A), 337-348
CODEN: ANTRD4; ISSN: 0250-7005

PB Anticancer Research

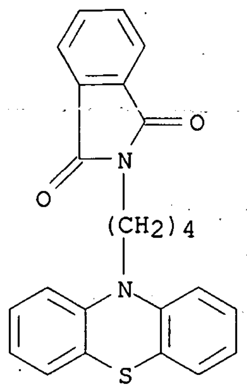
DT Journal

LA English

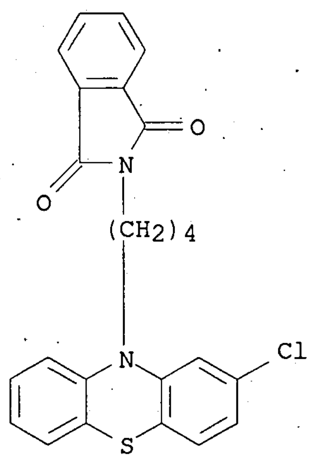
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(primary in vitro anticancer activity of "half-mustard type" phenothiazines in NCI's revised anticancer screening paradigm)

RN 180388-70-9 CAPLUS

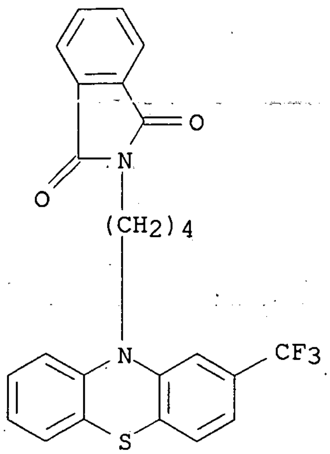
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)

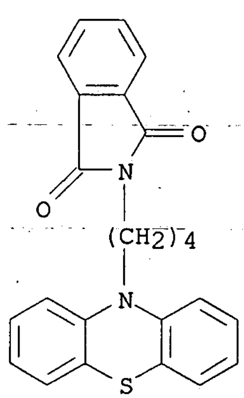


AB Some new phenothiazines have been synthesized on the basis of previous studies. The anticancer activity of "half-mustard type" phenothiazines was investigated on sixty different cancer cell lines in vitro. The percentage of growth (PG), 50% inhibition of growth (GI50), the tumor growth inhibition (TGI) and the concn. required for 50% lethality of cells (IC50) were examd. and calcd. in the presence of various (from 10-4 to 10-8 M) concns. of phenothiazine alkylurea derivs. The following cell lines were involved in the study: 6 leukemia, 9 non-small-cell lung cancer, 7 colon cancer, 6 central nervous system cancer, 8 melanoma, 6 ovarian cancer, 8 renal cancer, 2 prostate and 8 breast cancer cell lines. The anti-leukemic activity of four chloroethyl-substituted phenothiazine-alkylureas was shown by considerable growth inhibition, in the 10-5 M range, of the six different leukemia cell lines. The 50% inhibition of growth was nearly the same for the four compds. on all cell lines. Tumor growth inhibition (TGI) and IC50 value to cells varied from -4.0 to -4.66. The two derivs. with the butylene bridge were more effective than propylene linked compds. against the CCRP-CEM, HL60 (TB), K-562 and MOLT-4 cell lines. However, the anti-leukemic activity of the derivs. was nearly the same for RPMT 8226 and SR cell lines. The substituent at the 2- position of phenothiazine ring and the length of the linker between the side chain nitrogen and the phenothiazine ring system are apparently important for antileukemic activity. Four of the 9 non-small-cell lung cancer cell lines were sensitive, while the other 5 cell lines were not. The compds. had a slight growth inhibitory effect on colon cell carcinoma and melanoma cells in which case the butylene linker seemed to be more effective than the propylene linker. At the same time, all of the compds. were weak or mostly inactive on cancer cells from the central nervous system. One ovarian cancer line of the 6, the IGROVI was sensitive to butylurea phenothiazines, however, the other five were not sensitive at all. The difference in the sensitivity of various renal cell carcinomas was significant: 5 lines were not sensitive, three of them (786-0, RXF-393 and TK-10) were sensitive to only butylene-substituted phenothiazine-ureas, propylene substitution resulted in ineffective compds. The compds. were not able to inhibit the 2 prostate and 4 breast cancer cell lines, even at 10-4 M. It was interesting that propylene-linked ureas were more effective than butylene-linked derivs. on MCF-7, but butylene-linked derivs. were more effective than propylene-linked compds. on MDA MB-231 and MDA-N. In addn., MDA MB 435 was more sensitive to the trifluoromethyl derivs. than the compds. without

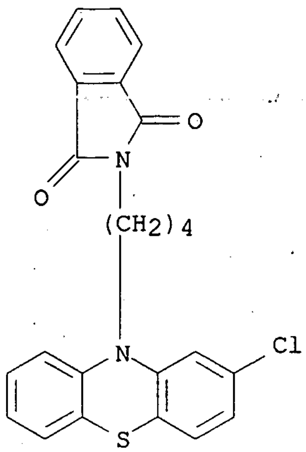
this substituent. Since the phthalimido-alkyl phenothiazines were not active at the first level of prescreen, these compds. were omitted from this study. The drug sensitivity of some cancer cell lines was not uniform for the different groups, therefore we postulate that the resistance can be related to some kind of (existing) drug-efflux mechanism. Apparently, the tumor specificity of phenothiazine alkylureas is more related to the leukemia specificity of alkylureas than to any CNS or lung specificity of phenothiazines.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

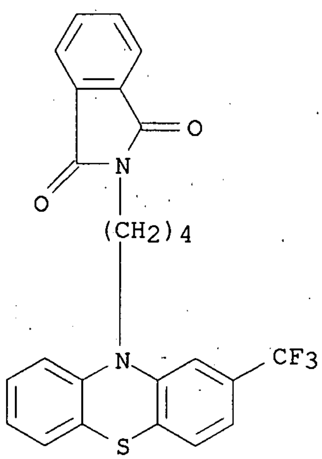
L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:200671 CAPLUS
DN 128:265747
TI Correlation between structure and diverse biological activities of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Satoh, Kazue; Sakagami, Hiroshi; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tokyo, 188, Japan
SO Anticancer Research (1997), 17(6D), 4403-4406
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(correlation between structure and diverse biol. activities of half-mustard type phenothiazines in relation to dipole moments and radical generation)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



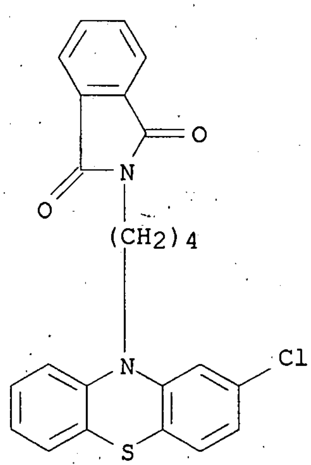
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



AB The structure and activity relation of fifteen "half-mustard type" phenothiazines and related compds. were investigated. These compds. did not show any direct bactericidal activity, possibly due to the lack of radical generation activity. Pretreatment with phenothiazines significantly reduced the lethality of Escherichia coli GN2411 infection, possibly due to activation of the host defense mechanism. Higher concns. of these compds. showed cytotoxic activity against several cultured tumor cell lines. However, no clear-cut relation was established between biol. activity and two dipole moments (.mu.g, .mu.e).

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49717 CAPLUS
DN 128:162543
TI Drug resistance reversal, antimutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Kawase, Masami; Hever, Aniko; Tanaka,

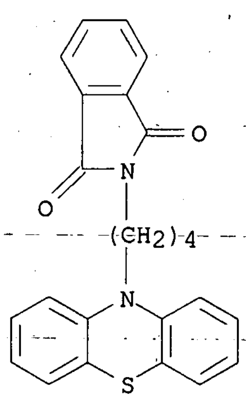
Masaru; Szabo, Diana; Nacsa, Janos; Yamanaka, Wataru; Kerim, Ablikim; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1997), 17(5A), 3537-3543
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-72-1**, 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]-
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(drug resistance reversal, antimutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines)
RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



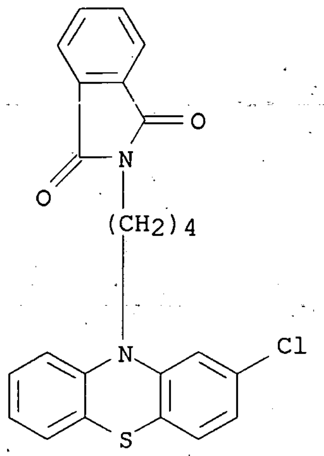
AB The effect of substituted phenothiazines was studied in three different systems; bacteria and cancer cells and reverse transcriptase enzyme of Moloney leukemia virus. F'lac and hemolysin plasmids were eliminated by some substituted phenothiazines from E. coli at a very low frequency. The same phenothiazine derivs. also were synergistic with tetracycline in bacteria and shown antimutagenic effect in Ames test. No mutagenic effects were obsd. in TA 98 strain of Salmonella typhimunium. Chloroethyl-substituted phenothiazines showed antimutagenicity equiv. to the parent compds.; however, phthalimido-substituted phenothiazines had higher antimutagenicity of 50%. P-glycoprotein responsible for multidrug resistance was also inhibited in tumor cells. The accumulation of the fluorescent rhodamine 123 in the phenothiazine treated multidrug resistant tumor cells was measured by flow cytometry. Some of the substituted phenothiazines were effective P-glycoprotein blockers, while some compds. had moderate activity, but others were without effect as compared to 5 .mu.M verapamil. On the basis of computer anal. there are some correlations between the biol. activities and the dipole moments, and entropy of the studied mols. Our results suggest that the inhibition of

Hly+ plasmid replication and P-glycoprotein function may depend partly on similar electronic properties of the studied phenothiazine derivs. The activity of Moloney leukemia virus reverse transcriptase was inhibited by the substituted phenothiazines, however, no basic differences were found in the activities of phthalimido- and chloroethyl substituted phenothiazines.

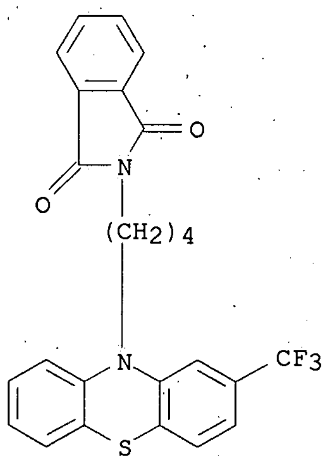
L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49699 CAPLUS
DN 128:175800
TI The in vitro antitumor assay of "half-mustard type" phenothiazines in screens of AIDS-related leukemia and lymphomas
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3425-3429
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9**, D 681648 **180388-72-1**, D 681650
180388-74-3, D 681652
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antitumor assay of half-mustard type phenothiazines in screens of AIDS-related leukemia and lymphomas in relation to structure)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



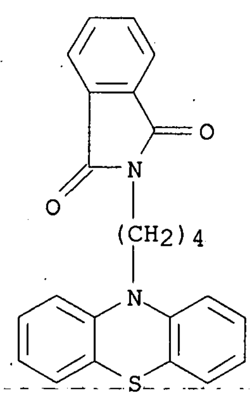
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



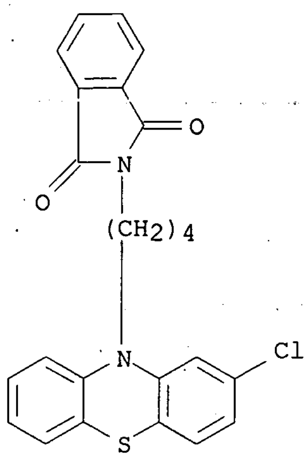
AB Twelve different "half-mustard type" phenothiazines were newly synthesized and tested on seven AIDS-related lymphoma (ARL) tumor cell lines, one leukemia CCRF-CEM cell culture and five different lymphoma lines; RL, KD488, AS283, PA682 and SU-DHL-7 cell lines. The alkylene-urea substituted phenothiazines affected the growth and inhibited the growth rate of AIDS-related lymphoma cells. The Cl-substituent at the 2-position was more effective than the CF3 substitution. In AIDS-related leukemia, also the compds. with Cl at the 2-position with propylene or butylene linkers, -(CH2)3- and -(CH2)4-, resp., were more effective than the CF3 substituted compds. Two of the six phenothiazine-substituted alkyl-urea derivs., i.e., 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propyl-1-urea (GI50=-5.66, TGI=-5.04) and 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butyl-1-urea (GI50=-5.61, TGI=-5.12) exhibited antitumor activity for AIDS-related leukemia and five AIDS-related lymphomas. The trifluoromethyl-substituted derivs. were not as effective on AIDS-related tumor cell lines. Apparently, the substituent at the

2-position on the phenothiazine and the alkylene no. of the linker attached to the nitrogen of the phenothiazine ring have an important role in the compd.'s antitumor effects on AIDS-related leukemia and lymphomas.

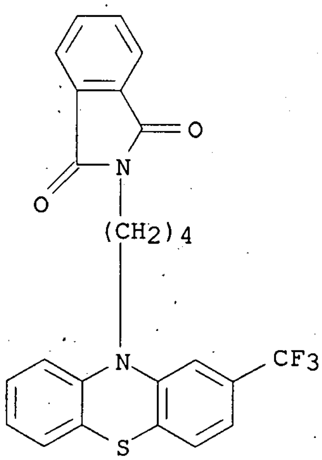
L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49698 CAPLUS
DN 128:162631
TI The primary in vitro antitumor screening of "half-mustard type" phenothiazines
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Nacsa, Janos; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3409-3423
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9**, D 681648 **180388-72-1**, D 681650
180388-74-3, D 681652
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(the primary in vitro antitumor screening of "half-mustard type" phenothiazines)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



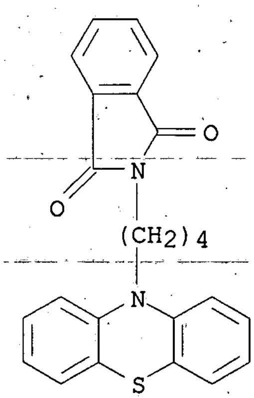
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



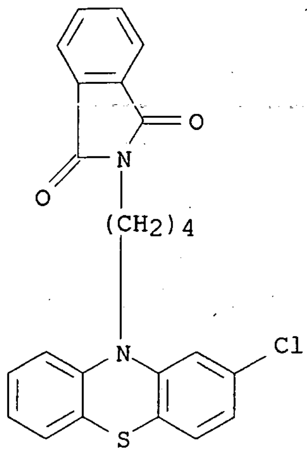
AB The antitumor effects of "half-mustard type" phenothiazines were studied on 57 different tumor cell lines, including leukemias, non-small lung cancer, colon, central nervous system, ovarian, renal, breast, and prostate cancer, as well as melanoma cell cultures. Alkyl-urea derivs. of phenothiazines displayed in vitro antitumor activity. The phenothiazine phthalimido derivs. (1-6) were not active on the majority of cancer cell cultures. In contrast, propylureas (9, 11) were active against some leukemia cell types. Only two compds. with the butylene [(CH2)4] linker (10, 12) were active against non-small lung cancer cells. Compds. contg. the propylene linker were less effective. On colon cancer lines, tumor cells from the central nervous system and on melanoma cells the same compds. were effective, however, having substituents at the 2-position of phenothiazine seems to be important. Surprisingly, the majority of ovarian cancer cell lines (except one type, IGROVI) and five of eight renal cancer lines were not sensitive to these phenothiazine derivs. The two butylene linked phenothiazine ureas (10, 12) had moderate

antiproliferative action on two renal cancer cell lines. The prostate cancer and some breast cancer cell lines were not sensitive. Nevertheless some breast cancer cell lines were apparently sensitive to CF3-substituted phenothiazine alkylureas. On the basis of these expts. one may postulate that in the case of insensitive cells an mdr-gene encoded multidrug resistance efflux pump is responsible for the resistance. The selectivity or organ cell specificity of the effective phenothiazines will be targeted for improvement in further studies, in order to avoid the general cytotoxic effects of "half mustard type" phenothiazines.

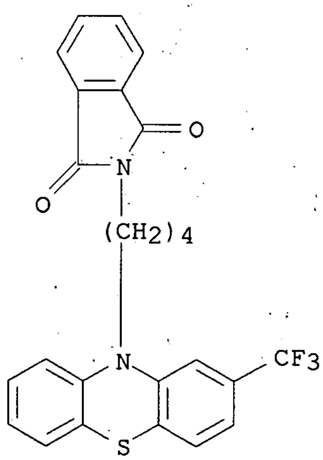
L4 ANSWER 11 OF 20 CAPLUS
AN 1996:703922 CAPLUS
DN 126:26380
TI Synthesis and antitumor activity of 1-[2-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl]-1-ureas as potent anticancer agents
AU Motohashi, Noboru; Kawase, Masami; Kurihara, Teruo; Hever, Aniko; Nagy, Szilvia; Ocsocvszki, Imre; Tanaka, Masaru; Molnar, Joseph
CS Department Medicinal Chemistry, Meiji College Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1996), 16(5A), 2525-2532
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9P 180388-72-1P 180388-74-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and antitumor activity of [(chloroethyl)(substituted-phenothiazinyl)alkyl]ureas in relation to structure)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



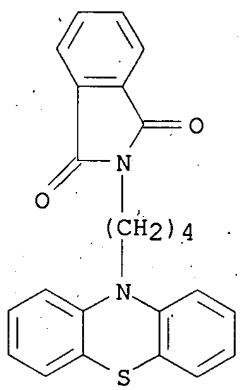
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



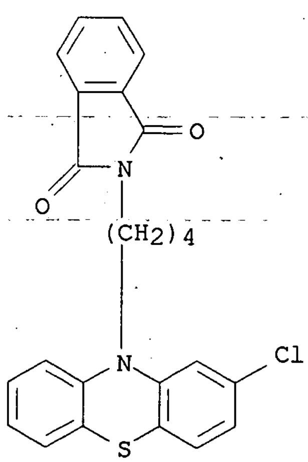
AB 10-[N-(Phthalimido)alkyl]-2-substituted-10H-phenothiazines and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were synthesized and found to have antiproliferative effects on human HEp-2 and L5178Y cell cultures. The multi-drug resistant subline of mouse lymphoma was sensitive to the reversal effects of some 10-[N-(phthalimido)alkyl]-2-substituted-10H-phenothiazines, while 1-(2-chloro-ethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were less effective but had a similar degree of antiproliferative effect on both cell lines.

L4 ANSWER 12 OF 20 CAPLUS
AN 1996:518725 CAPLUS
DN 125:211824
TI Antitumor activity of phenothiazine-related compounds
AU Nagy, Sylvia; Argyelan, George; Molnar, Joseph; Kawase, Masami; Motohashi, Noboru

CS Faculty Medicine, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.
SO Anticancer Research (1996), 16(4A), 1915-1918
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phenothiazine deriv. antitumor activity)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)

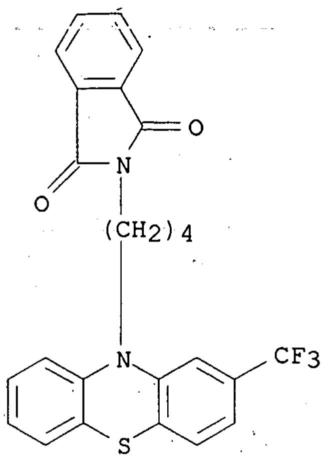


RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



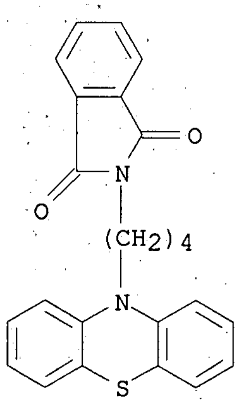
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-

yl]butyl]- (9CI) (CA INDEX NAME)

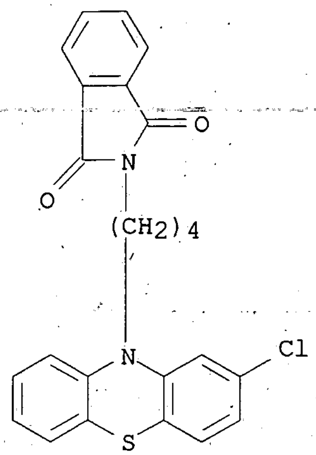


AB One of the biggest challenges in health care is the fight against tumors. Some phenothiazines have antitumor activity on HEp-2 tumor cells. In this study, we tested the antitumor effects of three series such as 10-nonsubstituted phenothiazines, 10-[n-(phthalimido)alkyl]-2-substituted-10H-phenothiazines and 1-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas with H, Cl and CF3 substitution at position C2. The TCID50 of phenothiazines was affected by the H, Cl and CF3 at C2. The trifluoromethyl deriv. of phenothiazine showed potent (R = CF3, TCID50 = 4.7 .mu.g) activity, whereas the chlorine deriv. of phenothiazine (R = Cl, TCID50 = 62.5 .mu.g) had a relatively weak effect. In the group of 10-[n-(phthalimido)alkyl]-2-substituted-10H-phenothiazines, 10-[3-(phthalimido)propyl]-10H-phenothiazine (R = H, n = 3, TCID50 = 11.5 .mu.g), 10-[4-(phthalimido)butyl]-10H-phenothiazine (R = H, n = 4, TCID50 = 7.8 .mu.g) and 10-[3-(phthalimido)propyl]-2-trifluoromethyl-10H-phenothiazine (R = CF3, n = 3, TCID50 = 11.5 .mu.g) were very effective. On the other hand, TCID50 of 10-[3-(phthalimido)propyl]-2-chloro-10H-phenothiazine (R = Cl, n = 3, TCID50 = 75.0 .mu.g), 10-[4-(phthalimido)butyl]-2-chloro-10H-phenothiazine (R = Cl, n = 4, TCID50 = 31.3 .mu.g) and 10-[4-(phthalimido)butyl]-2-trifluoromethyl-10H-phenothiazine (R = CF3, n = 4, TCID50 = 50.0 .mu.g) were about 4-8 times less effective than 10-[4-(phthalimido)butyl]-10H-phenothiazine (R = H, n = 4, TCID50 = 7.8 .mu.g). Among six 1-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas, two chlorine compds. such as 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propyl-1-urea (R = Cl, n = 3, TCID50 = 6.3 .mu.g), 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butyl-1-urea (R = Cl, n = 4, TCID50 = 7.8 .mu.g), and 1-(2-chloroethyl)-3-(2-trifluoromethyl-10H-phenothiazin-10-yl)butyl-1-urea (R = CF3, n = 4, TCID50 = 7.8 .mu.g) were significantly active. Tests showed that the substitution at 2C position apparently affected the anti-HEp-2 tumor cell activity; that the length of the aliph. side chain at 10N contributes to the anti-tumor activity; and that the TCID50 values of the derivs. with a butylene group (-C4H8-) were lower than those with propylene group (-C3H6-) except 10-[4-(phthalimido)butyl]-2-trifuoromethyl-10H-phenothiazine and 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10yl) butyl-1-urea.

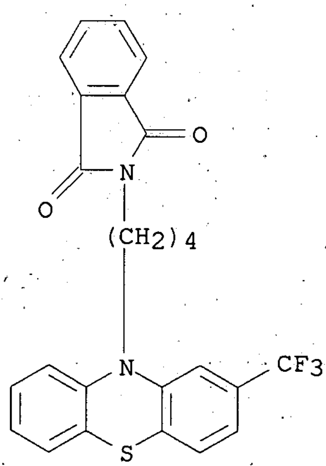
L4 ANSWER 13 OF 20 CAPLUS
AN 1996:472497 CAPLUS
DN 125:211925
TI Immunomodulating activities on cellular cytotoxicity and the blast transformation of human lymphocytes by 10-n-(phthalimido) alkyl-2-substituted-10H-phenothiazines and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas
AU Petri, Ilidiko B.; Szekeres, Eva; Varga, Eva; Berek, Imre; Molnar, Joseph; Berek, Livia; Kawase, Masami; Motohashi, Noboru
CS Blood Transfusion Centre, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.
SO Anticancer Research (1996), 16(3A), 1247-1250
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulating activities on cellular cytotoxicity and blast transformation of human lymphocytes by)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



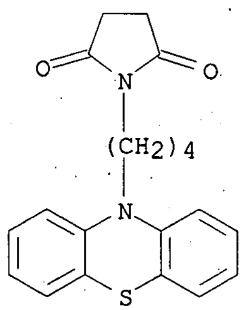
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



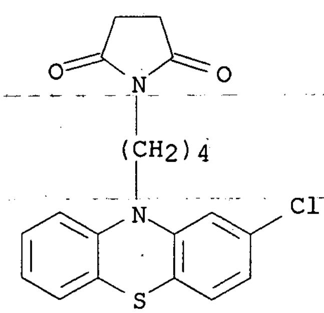
AB Phenothiazines, 10-n-(phthalimido)alkyl-2-substituted-10H-phenothiazines, and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were investigated for their effects on antibody-dependent cellular cytotoxicity (ADCC), natural killer (NK) cells and the blast transformation of human peripheral blood mononuclear cells. All of the compds. dose-dependently suppressed mitogen stimulated T cell proliferation. In contrast, a strong enhancing effect on NK cell activity was detected mostly in the case of 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-10-ureas and their related compds. The stimulating effect directly influenced the NK cells and was demonstrated at all tested concns.

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:239126 CAPLUS
DN 124:332043
TI Induction of DNA fragmentation in human myelogenous leukemic cell lines by

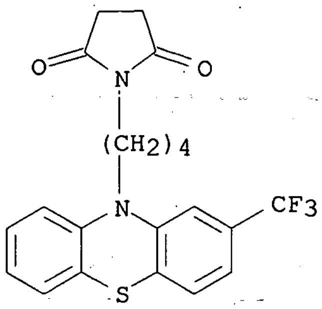
phenothiazine-related compounds
AU Sakagami, Kiroshi; Takahashi, Hideo; Yoshida, Hiroshi; Yamamura, Mitsuhisa; Fukuchi, Kunihiko; Gomi, Kunihide; Motohashi, Noboru; Takeda, Minoru
CS School Medicine, Showa University, Tokyo, 142, Japan
SO Anticancer Research (1995), 15(6B), 2533-40
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **176657-40-2 176657-42-4 176657-44-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(induction of DNA fragmentation in human myelogenous leukemic cell lines by phenothiazine-related compds.)
RN 176657-40-2 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 176657-42-4 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 176657-44-6 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)

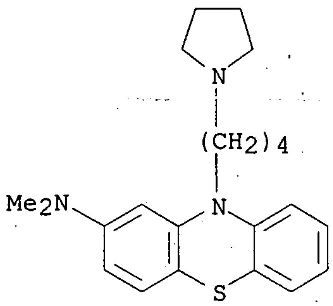


AB A series of phenothiazine, benzo[a]phenothiazine and benz[c]acridine derivs. were compared for their ability to induce nucleosome-sized DNA fragmentation (a biochem. hallmark of apoptosis), using agarose gel electrophoresis and a fluorescence activated cell sorter. Significant DNA fragmentation-inducing activity was detected in 12H-benzo[a]phenothiazine, 5-oxo-5H-benzo[a]phenothiazine and 9-methyl-12H-benzo[a]phenothiazine, which induced the monocytic differentiation of human myelogenous leukemic cell lines. On the other hand, an other three benzo[a]phenothiazines, six 10-[n-(phthalimido)alkyl]2-substituted-10H-phenothiazines, six 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas, and twelve benz[c]acridines showed little or no DNA fragmentation-inducing activity. Active benzo[a]phenothiazines induced DNA fragmentation in four human myelogenous leukemic cell lines (HL-60, ML-1, U-937, THP-1), but not in human T-cell leukemic MOLT-4 and erythroleukemic K-562 cell lines, which were also resistant to other apoptosis-inducing agents. Ca2+-depletion from the culture medium did not significantly affect their DNA fragmentation-inducing activity. The differentiation and apoptosis-inducing activity of benzo[a]phenothiazines have an important role for their medicinal efficacy.

L4 ANSWER 15 OF 20 CAPLUS
AN 1962:483298 CAPLUS
DN 57:83298
OREF 57:16630g-i,16631a-d
TI Dimethylaminophenothiazines
IN Craig, Paul N.
PA Smith Kline & French Laboratories
SO 4 pp.
DT Patent
LA Unavailable

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 3047572		19620731	US	19581210

IT **95138-82-2**, Phenothiazine, 2-(dimethylamino)-10-[4-(1-pyrrolidinyl)butyl]-
(prepn. of)
RN 95138-82-2 CAPLUS
CN Phenothiazine, 2-(dimethylamino)-10-[4-(1-pyrrolidinyl)butyl]- (7CI) (CA INDEX NAME)



AB The title compds. were prepd. and found useful as tranquilizers, calmatives, antiemetics, and general central nervous system depressants. 4-Bromo-3-nitrodimethylaniline (84 g.) in 600 ml. alc. treated with an aq. alc. soln. of Na o-bromothiophenol, the mixt. refluxed 20 hrs., and the product crystd. gave 2'bromo-2-nitro-4-dimethylaminodiphenyl sulfide (I), m. 120-1.degree. (alc.). I (91.9 g.) in 690 ml. concd. HCl treated with 235 g. SnCl2, refluxed 4 hrs., made alk., and the mixt. extd. with hot C6H6 gave 2'-bromo-2-amino-4-dimethylaminodiphenyl sulfide (II), m. 126-7.degree.. II (49.5 g.), 28.8 g. anhyd. K2CO3, 8 g. CuI, and 2.88 g. Cu bronze powder refluxed 500 ml. HCONMe2 gave 2-dimethylaminophenothiazine(III),m. 157-8.degree.; HBr salt was made. III(19.5 g.) in 700 ml. xylene treated 80 min. under reflux with 4 g. NaNH2, then refluxed 6 hrs. with 12.4 g. 3-chloro-1-dimethylaminopropane in 50 ml. xylene, extd. with AcOH, neutralized, and taken up in C6H6 gave 10-(3-dimethylaminopropyl)-2-dimethylaminophenothiazine, b0.3-0.5 215-20.degree.; di-HCl salt m. 214-15.degree.. III (24.2 g.) and 2.4 g. LiNH2 in 100 ml. PhMe refluxed 1 hr., then 7 hrs. under N with 16.3 g. 2-chloro-1-diethylaminopropane gave 10(diethylaminoisopropyl)-2-dimethylaminophenothiazine; a maleic acid salt was obtained. III (48.4 g.) and 8.3 g. NaNH2 in 500 ml. xylene refluxed 1.5 hrs. under N, then 5 hrs. with 41.8 g. 3-chloro-2-methyl-1-(N-methylpiperazinyl)propane gave 10-[2-methyl-1-(N-methylpiperazinyl)propyl]-2-dimethylaminophenothiazine; HBr salt was made. III (12.1 g.) in 500 ml. xylene and 1.2 g. LiNH2 refluxed 2 hrs., then 5 hrs. with 10.4 g. 1-formyl-4-(3-chloropropyl)piperazine in 100 ml. xylene gave 10-(3-N-formylpiperazinyl)propyl)-2-dimethylaminophenothiazine (IV) as an oil. IV (38.7 g.) in 200 ml. alc. and 125 ml. H2O contg. 30 ml. 40% NaOH refluxed 2 hrs. gave 10-(3'-piperazinylpropyl)-2-dimethylaminophenothiazine (V) as an oil. V (55.2 g.), 19.6 g. .beta.-bromoethanol, and 21.6 g. K2CO3 in 700 ml. PhMe refluxed 6 hrs. gave 10-(3-(N-.beta.-hydroxyethylpiperazinyl)propyl)-2-dimethylaminophenothiazine (VI); acetate prepd. VI (20.6 g.) in 300 ml. C6H6 and 4 g. AcCl left 10 hrs. at room temp. and the oily base treated with ethereal HCl gave 10-[3-(.beta.-acetoxyethylpiperazinyl)propyl]-2-dimethylaminophenothiazine-HCl. V (18.4 g.), 8.8 g. 2-bromo-2'-hydroxyethyl ether, and 7.6 g. K2CO3 in 500 ml. xylene refluxed 15 hrs. gave 10-[3-(N-hydroxyethoxyethylpiperazinyl)propyl]-2-dimethylaminophenothiazine; tartrate salt prepd. III (60.5 g.) and 10.1 g. NaNH2 in 800 ml. xylene refluxed with gradual addn. of 55.6 g. 4-bromo-1-N-pyrrolidinylbutane gave 10-[4-(N-pyrrolidinylbutyl)]2-dimethylaminophenothiazine; bismethylenesalicylate salt prepd. V (11 g.) in 50 ml. HCONMe2 treated with 7.5 g. p-nitrophenethyl bromide in 10 ml. HCONMe2, stirred 6 hrs. at 95-105.degree., poured into 1600 ml. H2O, the mixt. made alk., extd. with CHCl3, washed, filtered, and evapd. gave 10-[3-(p-

nitrophenethylpiperazinyl)propyl]-2-dimethylaminophenothiazine (VII). VII (11.7 g.) in 300 ml. alc. and 0.3 g. PtO2 hydrogenated 1 hr. at 50 lb./sq. in. gave 10-[3-(p-aminophenethylpiperazinyl)propyl]-2-dimethylaminophenothiazine.

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8225 CAPLUS
DN 55:8225
OREF 55:1667a-c
TI Basic alkylthioalkyl esters of phenothiazine-10-carboxylic acid and their salts
IN Myers, Gorden S.; Davis, Martin A.
PA American Home Products Corp.
DT Patent
LA Unavailable
FAN.CNT 1

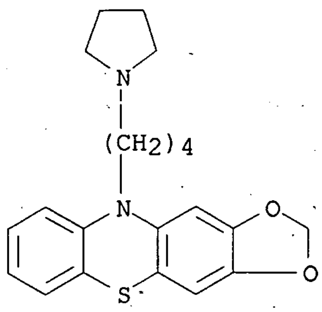
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2951077		19600830	US	

AB The title compds. were bacteriostatic agents. A soln. of .beta.-(diethylaminoethylthio)ethanol in 50 ml. pyridine was added to 26.1 g. phenothiazine-10-carboxylic acid chloride in 50 ml. dry pyridine. The mixt. was maintained at room temp. during addn. (20 min.), heated 30 min. at 25-90.degree., then for another 45 min. at 90.degree., cooled, and poured onto 400 ml. ice water. 2-(Diethylaminoethylthio)ethyl phenothiazine-10-carboxylate (I) was liberated from soln. by adding NaOH. I was extd. with ether, and washed with water repeatedly till free from pyridine. Evapn. of the solvent gave I as a dark oil. The citrate of I was prepd. by treating an ethereal soln. of I with an equal wt. of citric acid in acetone, m. 99-101.degree. (decompn.). Similarly were obtained: I.MeBr, m. 155-60.degree. (decompn.); 2-(dimethylaminoethylthio)ethyl phenothiazine-10-carboxylate maleate, m. 106-9.degree.; 2-(diisopropylaminoethylthio)ethyl phenothiazine-10-carboxylate citrate, m. 49-54.degree..

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8224 CAPLUS
DN 55:8224
OREF 55:1666f-i,1667a
TI Methylenedioxy-substituted phenothiazines
IN Gordon, Maxwell
PA Smith, Kline & French Laboratories
DT Patent
LA Unavailable
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2945031		19600712	US	

IT **112745-72-9**, 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]-
(prepn. of)
RN 112745-72-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (6CI) (CA INDEX NAME)



AB 6-Bromopiperonal (I) (m. 127-8.5.degree.) was prepd. from 300 g. piperonal and 120 ml. Br in 900 ml. HOAc. I (210 g.) was added in small portions to 1400 ml. concd. HNO3 while the temp. was kept at 25.degree. and the mixt. then decompd. with ice H2O to give 4-nitro-5-bromocatechol methylene ether (II), m. 88-9.degree.. A soln. of Na o-bromothiophenol (from 113.4 g. o-bromothiophenol, 500 ml. EtOH, 23.9 g. NaOH, and 25 ml. H2O) was added dropwise to 147.6 g. II in 1250 ml. hot EtOH, the mixt. refluxed 3 hrs., cooled, and filtered to give 4,5-methylenedioxy-2-nitro-2'-bromodiphenyl sulfide (III), m. 149-50.degree.. III (186 g.) was reduced with 426.6 g. SnCl2 and 675 ml. concd. HCl in 675 ml. EtOH to 2-amino-4,5-methylenedioxy-2'-bromodiphenyl sulfide (IV), m. 142-3.5.degree.. IV (3.6 g.), 1.56 g. anhyd. K2CO3, and 0.2 g. Cu powder in 45 ml. HCONMe2 was refluxed 6 hrs., filtered, and the filtrate dild. with H2O to ppt. 2,3-methylenedioxyphenothiazine (V), m. 202-3.5.degree.. V (24.3 g.) and 2.4 g. LiNH2 in 100 ml. dry toluene was refluxed 3 hrs., 13.3 g. 3-chloro-1-dimethylaminopropane in 10 ml. toluene added, the mixt. refluxed an addnl. 4 hrs., and from this mixt. an oil, 10-(3-dimethylaminopropyl)-2,3-methylenedioxyphenothiazine, isolated. 2,3-Methylenedioxyphenothiazines with the following substituents were also prepd.: 10-(diethylaminoisopropyl), 10-[2-methyl-1-(N-methylpiperazinyl)propyl], 10-[3-(N-formylpiperazinyl)propyl], 10-(3-piperazinylpropyl), 10-{3-[N-(.beta.-hydroxyethyl)piperazinyl]propyl}, 10-[3-(N-acetoxyethylpiperazinyl)propyl], 10-{3-[N-(hydroxyethoxyethyl)piperazinyl]propyl}, 10-(4-pyrrolidinylbutyl), 10-{3-[N-(p-nitrophenethyl)piperazinyl]propyl}, and 10-{3-[N-(p-aminophenethyl)piperazinyl]propyl}.

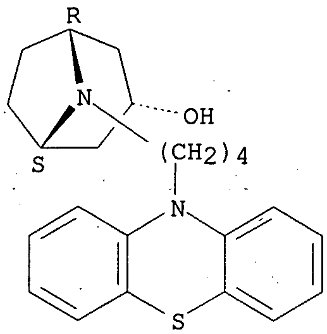
L4 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1958:104438 CAPLUS
DN 52:104438
OREF 52:18502d-i,18503a-b
TI N-[(10-Phenothiazinyl)-lower alkyl]-1,5-iminocycloalkanes
IN Zenitz, Bernard L.
PA Sterling Drug Inc.
DT Patent
LA Unavailable
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2838505		19580610	US	

IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-
123885-14-3, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-, acetate
(prepn. of)
RN 119148-95-7 CAPLUS

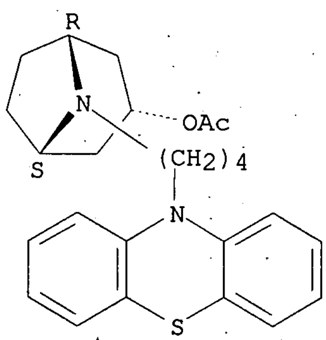
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

Relative stereochemistry.



RN 123885-14-3 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)-, acetate (6CI) (CA INDEX NAME)

Relative stereochemistry.

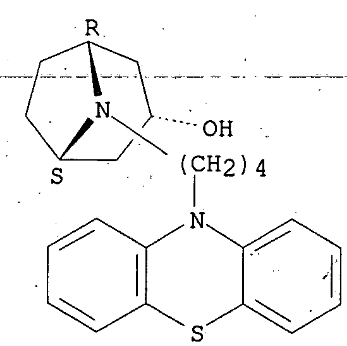


GI For diagram(s), see printed CA Issue.
AB Compds. (I) were prepd., where Y and Y' are the same or different H, halogen, lower-alkyl, or lower-alkoxy, A is a lower-alkylene group, n is 1 or 2, R is H, and R' is OH, O-Acyl, Cl, Br, or RR' is O. The I are useful as hypotensive agents, antinauseants, antipyretics, and sedatives. (All m.ps. are cor.). 10-(3-Chloropropyl)phenothiazine (13.8 g.) and 7.1 g. tropine (II) in 25 cc. HCONMe2 heated 24 hrs. on a steam bath, cooled in an ice bath, dild. with 50 cc. anhyd. Et2O, again cooled, the ppt. filtered off, triturated with Me2CO, the ppt. filtered off, and recrystd. 1st from 600 cc. iso-PrOH and then twice from 50 cc. abs. EtOH-75 cc. anhyd. Et2O with C gave 8.0 g. 8-[3-(10-phenothiazinzyl)propyl]-3-hydroxynartropine-MeCl, m. 224.5-5.5 (decompn.). Similarly were prepd. the following I (R = H in all cases) (Y, Y', A, n, R', m.p. given): H, H, (CH2)2, 1, OH, - (methochloride, m. 221-3.degree.); H, H, (CH2)2, 1, OAc, - (methochloride, m. 241-3.degree.); H, H, (CH2)2, 1, OAc, - (methochloride, m. 232.5-3.5.degree.); H, H, (CH2)2, 1, OH, 126-8.degree. (HCl salt, m. 246.5-8.5.degree.) [prepd. by treating II with H2O2 to obtain II oxide (III), m. 228-9.degree., treating III with Ac2O to obtain N,O-diacetylnortropine, and sapong. to nortropine (IV), m. 161-3.degree. (Me2CO), and treating with 10-(2-bromoethyl)phenothiazine]; H, H, (CH2)2,

1, OAc, 114-15.degree.; H, H, (CH2)3, 1, OH, 87.5-9.0.degree. (HCl salt, m. 177-9.degree.); H, H, (CH2)3, 1, OAc, 141.0-3.5.degree. (HCl salt, m. 218-20.degree.); H, H, (CH2)3, 1, O2CCH:CHPh, 139.0-41.5.degree.; H, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 151.5-3.5.degree.; H, H, (CH2)3, 1, OBz, 121-2.degree.; H, H, (CH2)4, 1, OH, 133-7.degree.; H, H, (CH2)4, 1, OAc, 115.5-18.0.degree.; H, H, (CH2)5, 1, OH, - (HCl salt, m. 192-4.degree.) [prepd. from p-MeC6H4SO3(CH2)5Cl, b0.14-0.23 148-53.degree., nD25 1.5157, by treating with phenothiazine to obtain 10-(5-chloropentyl)phenothiazine, b0.09 157.5-60.0.degree., nD25 1.6391, followed by treatment with IV]; 2-Cl, H, (CH2)3, 1, OH, 119.5-22.0.degree.; 2-Cl, H, (CH2)3, 1, O2CCH:CHPh, 130.5-1.5.degree.; 2-Cl, H, (CH2)3, 1, OBz, 94.0-8.5.degree.; 2-Cl, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 155-8.degree.; 3-Cl, H, (CH2)3, 1, OH, 146,5-8.5.degree. [prepd. from p-MeC6H4SO3(CH2)3Cl, b0.04 141-7.degree., nD25 1.6660, and (3-chloropropyl)phenothiazine to obtain 3-chloro-10-(3-chloropropyl)phenothiazine, m. 45.0-7.5.degree., and treatment with IV]; 3-Cl, H, (CH2)3, 1, OAc, 107.5-9.5.degree.; 3-Cl, H, (CH2)3, 1, OBz, 102.0-4.5.degree.; 3-Cl, H, (CH2)3, 1, O2CCH:CHPh, 114.5-15.5.degree.; 3-Cl, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 165.0-6.5.degree.; 2-Cl, H, (CH2)3, 1, OH, 96.5-101.degree. [prepd. from pseudonortropine (m. 132-4.degree.) and CO2 to obtain pseudonortropine carbamate, m. 141-2.degree., followed by treatment with 2-chloro-10-(3-chloropropyl)phenothiazine]. When n is 2 in I, the compds. are derivs. of granatanine.

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1957:73091 CAPLUS
DN 51:73091
OREF 51:13200a-d
TI Structure activity relationships of some phenothiazine-substituted nortropane derivatives
AU Long, J. P.; Lands, A. M.; Zenitz, B. L.
CS Sterling-Winthrop Inst., Rensselaer, NY
SO J. Pharmacol. Exptl. Therap. (1957), 119, 479-84
DT Journal
LA Unavailable
IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-
(pharmacology of)
RN 119148-95-7 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

Relative stereochemistry.

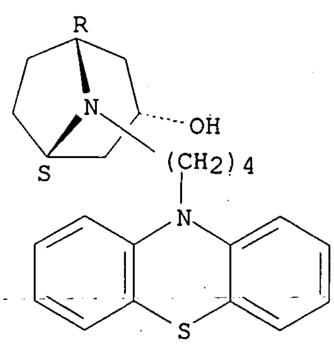


AB A series of 13 nortropane-substituted phenothiazine derivs. were

investigated for central-nervous-system activity (production of hypothermia in mice) and peripheral adrenolytic action (reversal of adrenaline effects in dogs). The compds. had a di-, tri-, tetra-, or pentamethylene bridge joining the phenothiazine N with the tropane N and had H, OH, or a 3,4,5-trimethoxybenzoxy radical in the 3-position of the tropane ring. In most respects the adrenolytic activity closely paralleled the central-nervous-system activity. The trans isomers showed higher activity than the cis isomers or the 3-dehydroxy derivs. The exptl. data support the hypophysis that a drug-receptor interaction is involved both centrally and peripherally, and that these receptors are quite similar with respect to the compds. studied. 2-Chloro substitution in the phenothiazine ring increases the central-nervous-system activity without a consistent alteration of the peripheral adrenolytic activity.

L4 ANSWER 20 OF 20 CAPLUS
AN 1957:73090 CAPLUS
DN 51:73090
OREF 51:13199i,13200a
TI Pharmacology of carbutamide
AU Root, Mary A.
CS Lilly Research Labs., Indianapolis, IN
SO J. Pharmacol. Exptl. Therap. (1957), 119, 468-78
DT Journal
LA Unavailable
IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-
(pharmacology of)
RN 119148-95-7 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

Relative stereochemistry.



AB Carbutamide is a sulfonylurea deriv. with low toxicity which causes hypoglycemia when given orally to normal animals. It is ineffective in alloxan-diabetic animals and in totally depancreatized dogs. If it is administered to diabetic animals being treated with insulin, their blood-glucose concns. and daily urinary sugar excretion are decreased below the levels found with insulin alone.

=> s l4 and antimalarial and humal
L5 0 L4 AND ANTIMALARIAL AND HUMAL

=> s l4 and antimalarial

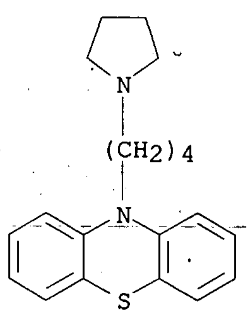
L6 3 L4 AND ANTIMALARIAL

=> d 16 fbib hitstr abs total

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2003:118638 CAPLUS
DN 138:153540
TI Preparation of aminobutylphenothiazines, -iminodibenzyls, and related compounds as chemosensitizing agents against chloroquine resistant plasmodium falciparum
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003032801	A1	20030213	US 2001-849400	20010507
				US 2001-849400	20010507

OS MARPAT 138:153540
IT **443309-35-1P**, 10-(4-Pyrrolidin-1-ylbutyl)phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of aminobutylphenothiazines, -iminodibenzyls, and related compds. as chemosensitizing agents against chloroquine resistant plasmodium falciparum)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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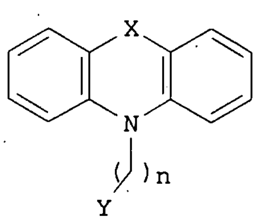


I

AB Title compds. [I; X = (substituted) alkyl, heteroatom; n = 4-6; Y = (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, NR1R2; R1, R2 = H, heteroatom, (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; each ring structure may be substituted], were prepd. Thus, 10-(4-pyrrolidin-1-ylbutyl)phenothiazine (general prepn. given) at 50 ng/mL completely restored the sensitivity of TM91C235 cells to chloroquine.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2002:868744 CAPLUS
DN 137:370096
TI Tricyclic N-(aminoalkyl)-substituted phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines, active as chemosensitizing agents against chloroquine-resistant Plasmodium falciparum, and methods of making and using thereof
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA United States Army Medical Research and Material Command, USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

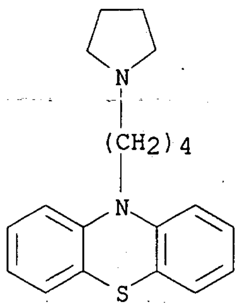
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002089810	A1	20021114	WO 2001-US14574	20010507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2001-US14574 20010507

OS MARPAT 137:370096
IT **443309-35-1P**, 10-[4-(Pyrrolidin-1-yl)butyl]phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines as **antimalarial** sensitizing agents for treatment of multidrug-resistant malaria with chloroquine and mefloquine)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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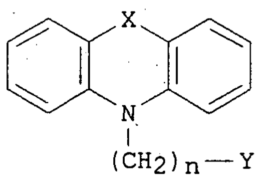

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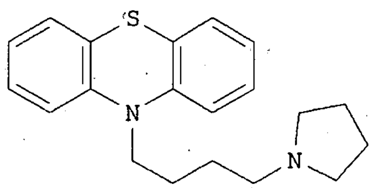


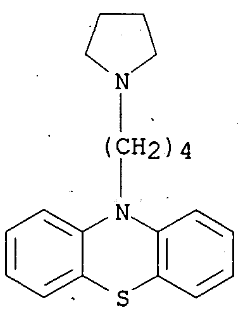
II

AB Title compds. I and pharmaceutically acceptable salts or prodrugs thereof are disclosed [wherein: X is a substituted or unsubstituted alkyl, a heteroatom, or 2 H atoms; n is 4, 5, or 6; Y is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or NR1R2; wherein R1 and R2 are each independently, H, a heteroatom, substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and wherein each ring structure is independently substituted or unsubstituted]. Also disclosed are chemosensitizing agents and methods of modulating, attenuating, reversing, or affecting a cell's or organism's resistance to a given drug such as an **antimalarial**. In particular, a group of compds. I were prepd. and shown to have improved anti-MDR (multidrug resistance) efficacy and reduced side effects (no data) in restoration of the clin. efficacy of **antimalarials** including mefloquine and chloroquine. Four of the compds. also showed moderate intrinsic **antimalarial** activity in the absence of chloroquine or mefloquine. Structure-activity relationships, e.g., regarding alkyl chain length, ring rigidity, and amino terminal size, are discussed. For instance, 4-chloro-1-butanol was converted to the THP ether (99%) and then used to N-alkylate phenothiazine (46%), followed by deprotection (100%), conversion of the resultant alc. to a chloride with SOCl2 (62%), and amination of the chloride (34%) to give the pyrrolidine deriv. II. At 50 ng/mL in vitro, II completely restored the sensitivity of TM91C235 cells [a highly drug-resistant malaria isolate from Thailand] to chloroquine, giving 99% cell growth suppression/inhibition. When tested on a different clone of Plasmodium falciparum, II gave superior MDR-reversing activity, with a fractional inhibitory concn. (FIC) of 0.21, using a 1:1 combination of chloroquine and II.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 2002:372411 CAPLUS
DN 137:109247
TI Design, Synthesis, and Evaluation of New Chemosensitizers in Multi-Drug-Resistant Plasmodium falciparum
AU Guan, Jian; Kyle, Dennis E.; Gerena, Lucia; Zhang, Quan; Milhous, Wilbur K.; Lin, Ai J.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, MD, 20910, USA
SO Journal of Medicinal Chemistry (2002), 45(13), 2741-2748
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 137:109247
IT **443309-35-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of **antimalarial** drug chemosensitizing aminoalkyl phenothiazines, benzazepines, and diphenylamines)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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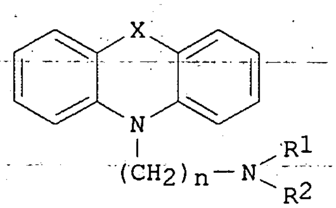
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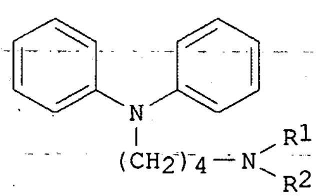
II

AB A series of new chemosensitizers (modulators) against chloroquine-resistant Plasmodium falciparum were designed and synthesized in an attempt to prep. modulators with enhancing drug-resistant reversing efficacy and minimal side effects. Phenothiazine, iminodibenzyl, and iminostilbene arom. amine ring systems I (X = S, CH2CH2, CH:CH; n = 4-6; R1, R2 = Me, Et, PhCH2; R1R2N = pyrrolinyl) and diphenylamines II (R1 = R2 = Et, R1R2N = pyrrolinyl) were examd. Various tertiary amino groups including either noncyclic or cyclic aliph. amines were introduced to

explore the steric tolerance at the end of the side chain. The new compds. showed better drug-resistant reversing activity in chloroquine-resistant than in mefloquine-resistant cell lines and were generally more effective against chloroquine-resistant P. falciparum isolates from Southeast Asian (W2 and TM91C235) than those from South America (PC49 and RCS). Structure-activity relationship studies revealed that elongation of the alkyl side chain of the mol. retained the chemosensitizing activity, and analogs with four-carbon side chains showed superior activity. Furthermore, new modulators with phenothiazine ring exhibited the best chemosensitizing activity among the four different ring systems examd. Terminal amino function has limited steric tolerance as evidenced by the dramatic lose of the modulating activity, when the size of substituent at the amino group increases. The fractional inhibitory concn. (FIC) index of the best new modulator I (X = S, n = 4, R1R2N = pyrrolinyl) is 0.21, which is superior to that of verapamil (0.51), one of the best-known multi-drug-resistant reversing agents. Some of the analogs displayed moderate intrinsic in vitro **antimalarial** activity against a W-2 clone of P. falciparum.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s antimalarials and human
L7         1368 ANTIMALARIALS AND HUMAN

=> s l7 and l4
L8            1 L7 AND L4

=> d l8 fbib hitstr abs total
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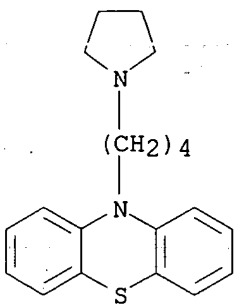
L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2003:118638 CAPLUS
DN 138:153540
TI Preparation of aminobutylphenothiazines, -iminodibenzyls, and related compounds as chemosensitizing agents against chloroquine resistant plasmodium falciparum
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003032801	A1	20030213	US 2001-849400	20010507
				US 2001-849400	20010507

OS MARPAT 138:153540
IT **443309-35-1P**, 10-(4-Pyrrolidin-1-ylbutyl)phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of aminobutylphenothiazines, -iminodibenzyls, and related compds. as chemosensitizing agents against chloroquine resistant plasmodium falciparum)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



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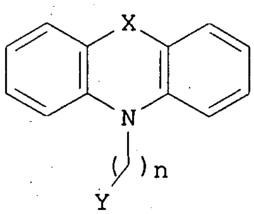

I

AB Title compds. [I; X = (substituted) alkyl, heteroatom; n = 4-6; Y = (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, NR1R2; R1, R2 = H, heteroatom, (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; each ring structure may be substituted], were prepd. Thus, 10-(4-pyrrolidin-1-ylbutyl)phenothiazine (general prepn. given) at 50 ng/mL completely restored the sensitivity of TM91C235 cells to chloroquine.

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=> d his

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L6              3 S L4 AND ANTIMALARIAL
L7           1368 S ANTIMALARIALS AND HUMAN
L8              1 S L7 AND L4

=> s l7 and 8-aminoquinoline
L9             23 L7 AND 8-AMINOQUINOLINE

=> s l7 andartesunate
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nested terms that are not separated by a logical operator.

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nested terms that are not separated by a logical operator.

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=> s 17 and proguanil
L15          69 L7 AND PROGUANIL

=> s 17 and chloroquine phosphate
L16           6 L7 AND CHLOROQUINE PHOSPHATE

=> d his

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     FILE 'REGISTRY' ENTERED AT 08:44:33 ON 21 MAY 2003
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L3           11 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 08:45:14 ON 21 MAY 2003
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L6            3 S L4 AND ANTIMALARIAL
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L10          79 S L7 AND ARTESUNATE
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L12         173 S L7 AND QUININE
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L15          69 S L7 AND PROGUANIL
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L16            6 S L7 AND CHLOROQUINE PHOSPHATE

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=> d l8 fbib hitstr abs total

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
AN   2003:118638  CAPLUS
DN   138:153540
TI   Preparation of aminobutylphenothiazines, -iminodibenzyls, and related
     compounds as chemosensitizing agents against chloroquine resistant
     plasmodium falciparum
IN   Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA   USA
SO   U.S. Pat. Appl. Publ., 27 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ---------------   ----  --------      ---------------   --------
PI   US 2003032801      A1   20030213      US 2001-849400    20010507
                                           US 2001-849400    20010507
OS   MARPAT 138:153540
IT   443309-35-1P, 10-(4-Pyrrolidin-1-ylbutyl)phenothiazine
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (claimed compd.; prepn. of aminobutylphenothiazines, -iminodibenzyls,
        and related compds. as chemosensitizing agents against chloroquine
        resistant plasmodium falciparum)
RN   443309-35-1  CAPLUS
CN   10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]-  (9CI)  (CA INDEX NAME)
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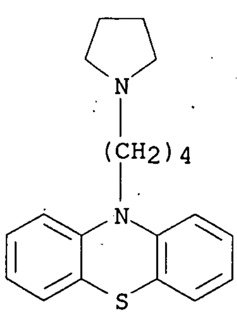

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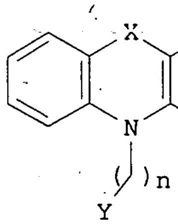

I

AB Title compds. [I; X = (substituted) alkyl, heteroatom; n = 4-6; Y = (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, NR1R2; R1, R2 = H, heteroatom, (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; each ring structure may be substituted], were prepd. Thus, 10-(4-pyrrolidin-1-ylbutyl)phenothiazine (general prepn. given) at 50 ng/mL completely restored the sensitivity of TM91C235 cells to chloroquine.

=> d l9 fbib hitstr abs total

L9 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2003:90670 CAPLUS
DN 138:180259
TI Effect of primaquine standard dose (15 mg/day for 14 days) in the treatment of vivax malaria patients in Thailand
AU Buchachart, K.; Krudsood, S.; Singhasivanon, P.; Treeprasertsuk, S.; Phophak, N.; Srivilairit, S.; Chalermrut, K.; Rattanapong, Y.; Supeeranuntha, L.; Wilairatana, P.; Brittenham, G.; Looareesuwan, S.
CS Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
SO Southeast Asian Journal of Tropical Medicine and Public Health (2001), 32(4), 720-726
CODEN: SJTMAK; ISSN: 0125-1562
PB SEAMEO-TROPMED Network
DT Journal
LA English
AB Primaquine (**8-aminoquinoline**), the only effective drug to prevent relapses of the persistent liver forms of Plasmodium vivax and Plasmodium ovale, can induce hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The severity varies considerably among affected individuals. Three hundred and sixty-four Plasmodium vivax cases (342 G6PD-normal and 22 G6PD-deficient) were given a 3-day course of chloroquine (total dose 1,500 mg) followed by primaquine 15 mg a day for 14 days and completed a 28-day follow-up. All G6PD-deficient patients were male; there were no relapses or serious adverse events during the study. Although a significant decrease in hematocrit levels and an increase in the percent redn. of hematocrit levels were obsd. on day 7 (34.9 .+-. 5.0 vs. 26.7 .+-. 5.4; (-1.2) .+-. 14.4 vs. (-24.5) .+-. 13.9 resp.) and on day 14 (35.7 .+-. 4.3 vs. 30.9 .+-. 3.1; 1.6 .+-. 17.8 vs. (-11.0) .+-. 19.3 resp.) blood transfusion was not required. Daily doses of 15 mg of primaquine for 14 days following a full course of chloroquine when prescribed to Thai G6PD deficient patients where Mahidol variant is predominant, are relatively safe.

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2002:634049 CAPLUS
DN 138:147050
TI New strategies in therapy to roll back malaria
AU Kaiser, A.; Maier, W.
CS Institut fuer Medizinische Parasitologie, Bonn, Germany
SO Deutsche Medizinische Wochenschrift (2002), 127(30), 1595-1600
CODEN: DMWOAX; ISSN: 0012-0472
PB Georg Thieme Verlag
DT Journal; General Review
LA German
AB A review on present therapeutic approaches to combat malaria. Advantages and disadvantages are discussed of chemotherapeutics relevant to clin. testing. The kind of action and half-lifes are listed of 4- and **8-aminoquinolines** and the phenanthrene deriv. halofantrine. Fixed combinations of artemether and lumefantrine, of atovaquone and proguanil, and of artesunate and mefloquine are described. New targets are characterized such as parasite-specific genes and the biosynthesis of fatty acids and polyamines of Plasmodium falciparum. The role of 1-deoxy-D-xylulose-5-phosphate reductoisomerase, of the bifunctional Orn/S-adenosylmethionine decarboxylase, and of deoxyhyposine synthase is discussed.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2002:93177 CAPLUS
DN 137:134512
TI A new primaquine analogue, Tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria
AU Shanks, G. Dennis; Oloo, Aggrey J.; Aleman, Gladys M.; Ohrt, Colin; Klotz, Francis W.; Braitman, David; Horton, John; Brueckner, Ralf
CS US Army Medical Research Unit, Nairobi, S. Afr.
SO Clinical Infectious Diseases (2001), 33(12), 1968-1974
CODEN: CIDIEL; ISSN: 1058-4838
PB University of Chicago Press
DT Journal
LA English
AB We tested tafenoquine (WR 238605), a new long-acting **8-aminoquinoline**, for its ability to prevent malaria in an area that is holoendemic for Plasmodium falciparum. In a double-blinded, placebo-controlled, randomized clin. trial in western Kenya, adult volunteers received a treatment course of 250 mg halofantrine per day for 3 days, to effect clearance of preexisting parasites. The volunteers were then assigned to 1 of 4 drug regimens: placebo throughout; 3 days of 400 mg (base) of tafenoquine per day, followed by placebo weekly; 3 days of 200 mg of tafenoquine per day, followed by 200 mg per wk; and 3 days of 400 mg of tafenoquine per day, followed by 400 mg per wk. Prophylaxis was continued for up to 13 wk. Of the evaluable subjects (223 of 249 randomized subjects), volunteers who received 400 mg tafenoquine for only 3 days had a protective efficacy of 68% (95% confidence interval [CI], 53%-79%), as compared with placebo recipients; those who received 200 mg per day for 3 days followed by 200 mg per wk had a protective efficacy of 86% (95% CI, 730%-93%); and those who received 400 mg for 3 days followed

by 400 mg per wk had a protective efficacy of 89% (95% CI, 77%-95%). A similar no. of volunteers in the 4 treatment groups reported adverse events. Prophylactic regimens of 200 mg or 400 mg of tafenoquine, taken weekly for .ltoreq.13 wk, are highly efficacious in preventing falciparum malaria and are well tolerated.

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2001:792223 CAPLUS
DN 135:348878
TI Therapeutic treatment and prevention of infections with a bioactive materials encapsulated within a biodegradable-biocompatible polymeric matrix
IN Setterstrom, Jean A.; Van Hamont, John E.; Reid, Robert H.; Jacob, Elliot; Jeyanthi, Ramasubbu; Boedeker, Edgar C.; Mcqueen, Charles E.; Jarboe, Daniel L.; Cassels, Frederick; Brown, William; Thies, Curt; Tice, Thomas R.; Roberts, F. Donald; Friden, Phil
PA United States of America as Represented by the Secretary of the Army, USA
SO U.S., 141 pp., Cont.-in-part of U.S. Ser. No. 590,973, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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FAN  1991:639773
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PI   WO 9113595         A1   19910919       WO 1991-US1777   19910315
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FAN  1993:154539
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PI   WO 9219263         A1   19921112       WO 1991-US3328   19910513
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FAN  1995:638679
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PI   WO 9726869        A1  19970731     WO 1996-US19440  19961118
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     AU 722884         B2  20000810
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FAN 1998:41700

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FAN 1998:405410

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FAN  2001:277930
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US 1984-590308 B119840316
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US 1996-590973 B219960124

AB Novel burst-free, sustained-release biocompatible and biodegradable microcapsules which can be programmed to release their active core for variable durations ranging from 1-100 days in an aq. physiol. environment are disclosed. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a pharmaceutically-acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99. Ampicillin microcapsules effectively prevented infection in 73% of rats whose wound were inoculated with ampicillin-resistant strains of Staphilococcus aureus, while systemic ampicillin failed in 100% of animals.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2001:321616 CAPLUS
DN 135:146843
TI Primaquine-induced hemolytic anemia: formation and hemotoxicity of the arylhydroxylamine metabolite 6-methoxy-8-hydroxylaminoquinoline
AU Bolchoz, Laura J. C.; Budinsky, Robert A.; McMillan, David C.; Jollow, David J.
CS Department of Pharmacology, Medical University of South Carolina, Charleston, SC, USA
SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(2), 509-515
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Primaquine is an important antimalarial agent because of its activity against exoerythrocytic forms of Plasmodium spp. However, methemoglobinemia and hemolytic anemia are dose-limiting side effects of primaquine therapy that limit its efficacy. These hemotoxicities are thought to be mediated by metabolites; however, the identity of the toxic species has remained unclear. Since N-hydroxy metabolites are known to mediate the hemotoxicity of several arylamines, the present studies were undertaken to det. whether 6-methoxy-**8-aminoquinoline** (6-MAQ), a known **human** metabolite of primaquine, could undergo N-hydroxylation to form a hemotoxic metabolite. When 6-MAQ was incubated with rat and **human** liver microsomes, a single metabolite was detected by high performance liq. chromatog. (HPLC) with electrochem. detection. This metabolite was identified as 6-methoxy-8-hydroxylaminoquinoline (MAQ-NOH) by HPLC and mass spectral analyses. As measured by decreased survival of 51Cr-labeled erythrocytes in rats, MAQ-NOH was hemolytic in vivo. Furthermore, in vitro exposure of 51Cr-labeled erythrocytes to MAQ-NOH caused a concn.-dependent decrease in erythrocyte survival (EC50 of 350 .mu.M) when the exposed cells were returned to the circulation of isologous rats. MAQ-NOH also induced the formation of metHb when incubated with suspensions of rat erythrocytes. These data indicate that 6-MAQ can be metabolized to MAQ-NOH by both rat and **human** liver microsomes and that MAQ-NOH has the requisite

properties to be a hemotoxic metabolite of primaquine. The contribution of MAQ-NOH to the hemotoxicity of primaquine in vivo remains to be assessed.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 2000:98342 CAPLUS
DN 132:131849
TI Poor gametocytocidal activity of 45 mg primaquine in chloroquine-treated patients with acute, uncomplicated, Plasmodium falciparum malaria in Mumbai (Bombay): an issue of public-health importance
AU Gogtay, N. J.; Chogle, A. R.; Sorabjee, J. S.; Marathe, S. N.; Kshirsagar, N. A.
CS Department of Clinical Pharmacology, Seth G. S. Medical College and K. E. M. Hospital, Mumbai, 400 012, India
SO Annals of Tropical Medicine & Parasitology (1999), 93(8), 813-816
CODEN: ATMPA2; ISSN: 0003-4983
PB Carfax Publishing
DT Journal
LA English
AB In the city of Mumbai (formerly Bombay), chloroquine (CQ) continues to be recommended as the drug of first choice for the treatment of Plasmodium vivax and P. falciparum infections, even though > 50% of local isolates of P. falciparum are resistant to it. Primaquine, an **8-aminoquinoline** is also given to patients with falciparum malaria, in a single, 45-mg dose, to kill the gametocytes and so reduce transmission. The gametocytocidal activity of supervised primaquine (45 mg given on day 8) was investigated in 90 patients who had been treated with CQ Of these, 15 were found to be CQ-sensitive patients, 61 were resistant (49, eight and four considered RI, RII and RIII, resp.) and 14 were lost before completion of the follow-up. The mean (S.D.) baseline gametocytemias in the CQ-sensitive and RI-resistant cases were 665.1 (411.3) and 1537.4 (1045.5)/.mu.l, resp. Despite supervised primaquine treatment, four of the 15 CQ-sensitive patients and 32 of the 49 patients found to be RI-resistant had gametocytes on day 29. There therefore appears to be a need to review the current, gametocytocidal, primaquine-dosage schedule and to re-treat patients who remain gametocytemic with higher doses of primaquine, as an important, transmission-blocking strategy.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1999:121930 CAPLUS
DN 130:332086
TI Chemotherapy of malaria
AU Ridley, Robert G.; Hudson, Alan T.
CS Pharmaceuticals Division, Department PRPI-D, F. Hoffmann-La Roche, Basel, CH-4070, Switz.
SO Current Opinion in Infectious Diseases (1998), 11(6), 691-705
CODEN: COIDE5; ISSN: 0951-7375
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
AB A review with 145 refs. Clin. trials continue to provide evidence for the efficacy of semi-synthetic artemisinin derivs., and the novel fixed dose

combination therapies Malarone, co-artemether and chlorproguanil-dapsone. Single agents under development include the **8-aminoquinoline** etaquine, pyronaridine and azithromycin. Preclin. interest in synthetic endoperoxides and quinoline analogs remains high and a significant is also being made in natural product chem. Dihydrofolate reductase remains a mol. drug target of interest, whereas phospholipid metab. represents a new approach. Genomic information is likely to produce many new drug targets for exploration in the coming decade.

RE.CNT 145 THERE ARE 145 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1999:20958 CAPLUS
DN 130:204709
TI Cytochrome 1A1 induction by primaquine in **human** hepatocytes and HepG2 cells: absence of binding to the aryl hydrocarbon receptor
AU Fontaine, Frank; Delescluse, Chantal; De Sousa, Georges; Lesca, Pierre; Rahmani, Roger
CS Laboratoire de Pharmaco-Toxicologie cellulaire et moleculaire, INRA, Antibes, Fr.
SO Biochemical Pharmacology (1999), 57(3), 255-262
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Malaria remains the most prevalent infectious disease of tropical and subtropical areas of the world. It represents a crucial problem in public health care, affecting 750 million people annually, of whom at least two million die. Various **antimalarials** currently used were studied for their capability to induce expression of the cytochrome P 450 1A1 (CYP1A1) gene, an enzyme that plays an important role in the activation of xenobiotics to genotoxic derivs. Studies on **human** hepatocytes and HepG2 cell lines showed that primaquine was capable of dose dependently increasing both the ethoxyresorufin-O-deethylase activity and CYP1A1 mRNAs, suggesting a transcriptional activation of this gene. Moreover, .alpha.-naphthoflavone, a partial aryl hydrocarbon receptor (AhR) antagonist, and 8-methoxypsoralen, which interferes with the binding of activated AhR to the xenobiotic responsive element, were shown to suppress CYP1A1 induction when added to the cultures. However, neither primaquine nor its metabolites were able to displace [3H]2,3,7,8-tetrachlorodibenzo-p-dioxin from AhR in competitive binding studies using 9S-enriched fractions of **human** cytosol. These data, together with the induction of CYP1A1 promoter-directed chloramphenicol acetyl transferase gene expression, suggest that CYP1A1 induction involves the participation of the AhR but not a direct primaquine-receptor interaction. This supports the notion that an alternative ligand-independent mechanism has to be considered. Given the pharmaco-toxicol. significance of CYP1A1 induction, these findings may have important implications in the treatment of malaria with primaquine and new analogs.

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1998:527193 CAPLUS
DN 129:166193
TI Therapeutic treatment and prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible polymeric

matrix
IN Setterstrom, Jean A.; Van Hamont, John E.; Reid, Robert H.; Jacob, Elliot; Jeyanthi, Ramasubbu; Boedeker, Edgar C.; McQueen, Charles E.; Tice, Thomas R.; Roberts, F. Donald; Friden, Phil
PA United States Dept. of the Army, USA; Van Hamont, John E.; et al.
SO PCT Int. Appl., 363 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9832427	A1	19980730	WO 1998-US1556	19980127

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	US 6309669	B1	20011030	US 1997-789734	19970127
				US 1984-590308 B1	19840316
				US 1992-867301 A2	19920410
				US 1995-446148 A2	19950522
				US 1995-446149 B2	19950522
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	AU 9863175	A1	19980818	AU 1998-63175	19980127
				US 1997-789734 A	19970127
				WO 1998-US1556 W	19980127

PATENT FAMILY INFORMATION:
FAN 1991:639773

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9113595	A1	19910919	WO 1991-US1777	19910315

W: AU, CA, FI, JP, NL, NO
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
				US 1990-493597 A	19900315
	AU 9175589	A1	19911010	AU 1991-75589	19910315
				US 1990-493597 A	19900315
				WO 1991-US1777 A	19910315

FAN 1993:154539

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9219263	A1	19921112	WO 1991-US3328	19910513

W: AU, CA, FI, JP, NL, NO
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

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				US 1991-690485 A	19910424
	AU 9183036	A1	19921221	AU 1991-83036	19910513
				US 1991-690485 A	19910424
				WO 1991-US3328 A	19910513

FAN 1995:638679

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PI	US 5417986	A	19950523	US 1992-867301	19920410
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                                           US 1990-493597 B219900315
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                                           US 1992-867301 A219920410
     US 5762965         A     19980609     US 1996-598874   19960209
                                           US 1984-590308 B119840316
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                                           US 1995-446149 A219950522
     US 6309669         B1    20011030     US 1997-789734   19970127
                                           US 1984-590308 B119840316
                                           US 1992-867301 A219920410
                                           US 1995-446148 A219950522
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                                           US 1996-590973 B219960124
FAN  1997:513551
     PATENT NO.         KIND  DATE         APPLICATION NO.  DATE
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PI   WO 9726869         A1    19970731     WO 1996-US19440  19961118
         W:  AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,
             ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT,
             LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG,
             KZ, MD, RU, TJ, TM
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,
             MR, NE, SN, TD, TG
                                           US 1996-590973 A 19960124
     CA 2216371         AA    19970731     CA 1996-2216371  19961118
                                           US 1996-590973 A 19960124
     AU 9714104         A1    19970820     AU 1997-14104    19961118
     AU 722884          B2    20000810
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                                           WO 1996-US19440W 19961118
     EP 817619          A1    19980114     EP 1996-944247   19961118
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
                                           US 1996-590973 A 19960124
                                           WO 1996-US19440W 19961118
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     JP 11509862        T2    19990831     JP 1996-526833   19961118
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				US 1996-590973	A 19960124
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FAN 1997:805549

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5693343	A	19971202	US 1994-242960	19940516
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				US 1990-493597	B219900315
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				US 1984-590308	A219840316
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				US 1990-521945	B219900511
				US 1991-690485	B219910424
				US 1991-805721	B219911121
	US 5762965	A	19980609	US 1996-598874	19960209
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				US 1991-690485	B219910424
				US 1991-805721	B219911121
				US 1992-867301	A219920410
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				US 1995-446149	A219950522
	US 5705197	A	19980106	US 1996-698896	19960816
				US 1994-242960	A219940516
	US 6447796	B1	20020910	US 1997-920326	19970821
				US 1994-242960	A219940516
				US 1995-446148	A219950522
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				US 1996-698896	A219960816
				US 1997-789734	A219970127

FAN 1998:41700

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5705197	A	19980106	US 1996-698896	19960816
				US 1994-242960	A219940516
	US 5693343	A	19971202	US 1994-242960	19940516
				US 1984-590308	A219840316
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				US 1990-521945	B219900511
				US 1991-690485	B219910424
				US 1991-805721	B219911121
				US 1992-867301	A219920410
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				US 1995-446148	A219950522
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				US 1996-590973	B219960124
				US 1996-675895	A219960705
				US 1996-698896	A219960816
				US 1997-789734	A219970127

FAN 1998:405410

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5762965	A	19980609	US 1996-598874	19960209
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				US 1990-521945	B219900511
				US 1991-690485	B219910424
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				US 1992-867301	A219920410
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FAN 2001:277930

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PI	US 6217911	B1	20010417	US 1996-675895	19960705
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FAN 2001:792223

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6309669	B1	20011030	US 1997-789734	19970127
				US 1984-590308	B119840316
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				US 1995-446148	A219950522
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				US 1996-590973	B219960124
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				US 1984-590308	A219840316
				US 1990-493597	B219900315
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				US 1991-690485	B219910424
				US 1991-805721	B219911121
	US 6410056	B1	20020625	US 1995-446148	19950522

				US 1984-590308	B219840316
				US 1990-493597	B219900315
				US 1994-209350	B219940107
	NZ 335409	A	20001222	NZ 1996-335409	19961118
				US 1996-590973	A 19960124
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	US 6447796	B1	20020910	US 1997-920326	19970821
				US 1994-242960	A219940516
				US 1995-446148	A219950522
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				US 1996-590973	B219960124
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	WO 9832427	A1	19980730	WO 1998-US1556	19980127

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

				US 1997-789734	A 19970127
	AU 9863175	A1	19980818	AU 1998-63175	19980127
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				WO 1998-US1556	W 19980127

FAN 2002:482993

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6410056	B1	20020625	US 1995-446148	19950522
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FAN 2002:688475

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				US 1994-242960	A219940516
	NZ 335409	A	20001222	NZ 1996-335409	19961118
				US 1996-590973	A 19960124
				NZ 1996-325561	A119961118
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				US 1984-590308	B119840316
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FAN 2003:334397

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				US 1996-590973	B219960124
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	NZ 335409	A	20001222	NZ 1996-335409	19961118
				US 1996-590973	A 19960124
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				US 1984-590308	B119840316
				US 1992-867301	A219920410
				US 1995-446148	A219950522
				US 1995-446149	B219950522
				US 1996-590973	B219960124

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules are disclosed which can be programmed to release their active core for variable durations ranging from 1-100 days in an aq. physiol. environment. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a pharmaceutically acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1998:348674 CAPLUS
DN 129:103800
TI First-time-in-**humans** safety and pharmacokinetics of WR 238605, a new antimalarial
AU Brueckner, Ralf P.; Lasseter, Kenneth C.; Lin, Emil T.; Schuster, Brian G.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC, USA
SO American Journal of Tropical Medicine and Hygiene (1998), 58(5), 645-649
CODEN: AJTHAB; ISSN: 0002-9637
PB American Society of Tropical Medicine and Hygiene
DT Journal
LA English
AB WR 238605 is an **8-aminoquinoline** drug currently under development for prophylaxis and treatment of malaria. Preclin. studies have demonstrated that it has greater efficacy and less toxicity compared with primaquine. In this first-time-in-**human** randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerance and pharmacokinetics, WR 238605 was administered to 48 men in single oral doses ranging from four to 600 mg (base). It was well tolerated, with gastrointestinal disturbances as possible side effects. Linear kinetics were demonstrated at these doses. WR 238605 has a long absorption phase and is slowly metabolized, with a tmax of 12 h and an elimination half-life of 14 days. These safety, efficacy and pharmacokinetic properties make this drug an excellent candidate for further testing as a prophylactic, radical curative, and terminal eradication drug.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1998:305646 CAPLUS
DN 129:92311
TI 4-aminoquinoline **antimalarials** enhance UV-B induced c-jun transcriptional activation
AU Nguyen, T. Q.; Capra, J. D.; Sontheimer, R. D.
CS Department of Dermatology, The University of Texas Southwestern Medical Center, Dallas, TX, 75235, USA
SO Lupus (1998), 7(3), 148-153
CODEN: LUPUES; ISSN: 0961-2033
PB Stockton Press
DT Journal
LA English
AB Previous work has documented that the earliest observable response in mammalian cells following UV irradn. is the activation of plasma membrane-assocd. Src tyrosine kinases. These mols. then trigger a signalling cascade that results in activation of the transcription factor AP-1 which subsequently transactivates the early immediate genes including c-jun. This pathway has been postulated to play a protective role against UV damage. As aminoquinoline **antimalarials** such as chloroquine are known to downregulate several photoinduced cutaneous disorders including LE-specific skin disease, we asked whether chloroquine might be capable of modulating this early limb of the UV light response. A431 cells (a **human** epidermal keratinocyte cell line) that had been transfected with a c-jun luciferase reporter gene construct were then

treated with physiol. relevant concns. of chloroquine followed by exposure to 0-125 J/m2 of UV-B from a bank of unfiltered FS20 lamps. Chloroquine pretreatment resulted in a dose-dependent increase in luciferase activity in permanently transfected A431 cells (luciferase activity was increased by 45% at 2.5 .times. 10-5 M chloroquine and 125 J/m2 of UV-B). Hydroxychloroquine pretreatment also resulted in an increase in luciferase activity. Primaquine, an **8-aminoquinoline**, did not influence the UV-B induced c-jun activity. Furthermore, chloroquine did not have a similar impact on HSP-70 gene activity during heat shock. These studies suggest that the beneficial effect of the 4-aminoquinoline **antimalarials** in various photodermatoses including cutaneous LE might result in part from the capacity of these drugs to enhance the protective early limb of the UV response.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1998:271708 CAPLUS
DN 129:36145
TI Prophylaxis of Plasmodium falciparum infection in a **human** challenge model with WR 238605, a new **8-aminoquinoline** antimalarial
AU Brueckner, Ralf P.; Coster, Trinka; Wesche, David L.; Shmuklarsky, Moshe; Schuster, Brian G.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC, 20307-5100, USA
SO Antimicrobial Agents and Chemotherapy (1998), 42(5), 1293-1294
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
AB The prophylactic efficacy of WR 238605, a primaquine analog, was studied with a **human** Plasmodium falciparum challenge model. A single oral dose of 600 mg, administered 1 day prior to challenge, successfully protected three of four subjects. The fourth subject developed mild, oligosymptomatic malaria on day 31, with drug concns. one-half of those in the protected individuals. WR 238605 appears to be a promising prophylactic drug for P. falciparum malaria.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1995:966060 CAPLUS
DN 124:20887
TI Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war
AU Greenwood, David
CS Wellcome Inst. History Med., London, NW1 2BE, UK
SO Journal of Antimicrobial Chemotherapy (1995), 36(5), 857-72
CODEN: JACHDX; ISSN: 0305-7453
PB Saunders
DT Journal; General Review
LA English
AB A review with 52 refs. Malaria has had an enormous impact on **human** history, not least in times of war. The disease has been treatable by a natural remedy, quinine, since the 17th century, but the prodn. of synthetic antimalarial agents was first achieved in Germany in

the wake of the Great War of 1914-1918, in which malaria had caused immense problems. In the 1920s research workers in the Bayer labs. of the IG Farbenindustrie consortium developed the **8-aminoquinoline** plasmoquine (the forerunner of primaquine). They went on to develop the acridine dye, atebrin (mepacrine) and the 4-aminoquinolines, Resochin (developed at the end of the Second World War, in America as chloroquine) and Sontochin. British attempts to match the advances achieved by the Germans were at first unproductive, partly because collaboration between academic and industrial organizations in the UK was beset by concerns over patent rights. However, with the outbreak of World War II, when supplies of **antimalarials** were scarce, ICI succeeded in the large-scale prodn. of mepacrine (essential to prosecution of the war, particularly in the Far East) and also initiated a program of collaborative research that eventually led to the discovery of proguanil (Paludrine); this, in its turn led to the diaminopyrimidine, pyrimethamine. A massive cooperative screening program in the USA during World War II eventually bore fruit in the realization of the therapeutic potential of chloroquine, and in the later development of amodiaquine and primaquine. Some of this work also influenced the subsequent discovery of mefloquine and halofantrine at the Walter Reed Army Institute of Research.

L9 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1995:778462 CAPLUS
DN 123:217615
TI Quantification of the individual enantiomer plasma concentrations of the candidate antimalarial agent N4-[2,6-dimethoxy-4-methyl-5-[(3-trifluoromethyl)phenoxy]-8-quinolinyl]- 1,4-pentanediamine (WR 238,605)
AU Karle, Jean M.; Olmeda, Raul; Freeman, Sandy G.; Schroeder, Alan C.
CS Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC, 20307, USA
SO Journal of Chromatography, B: Biomedical Applications (1995), 670(2), 251-7
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier
DT Journal
LA English
AB A high-performance liq. chromatog. method was developed to quantitate the plasma concns. of the individual enantiomers of a candidate **8-aminoquinoline** antimalarial agent WR 238,605 (I). The method employed one-step liq. extn. of a 0.5-mL plasma sample followed by direct injection of the ext. through a chiral column and detection by fluorescence. Quantification was achieved using an internal std. The limit of quantification was 10 ng/mL for each enantiomer. The method is sufficiently sensitive to quantitate the plasma concns. of both enantiomers for 30 days following a single oral dose of 400 mg of the antimalarial agent administered as the racemic succinate salt to healthy **human** male volunteers. In nearly all samples taken 12 h to 30 days post-dose from three subjects, the difference in the plasma concns. of the two enantiomers is less than 10%.

L9 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1992:15335 CAPLUS
DN 116:15335
TI Simultaneous modeling of the pharmacokinetics and methemoglobin pharmacodynamics of an **8-aminoquinoline** candidate antimalarial (WR 238605)
AU Brueckner, Ralf P.; Fleckenstein, Lawrence

CS Dep. Pharmacol., Walter Reed Army Inst. Res., Washington, DC, 20307-5100, USA
SO Pharmaceutical Research (1991), 8(12), 1505-10
CODEN: PHREEB; ISSN: 0724-8741
DT Journal
LA English
AB MetHb (MHb) formation can be a dose-limiting side-effect of **8-aminoquinoline antimalarials**. MHb may also protect against cyanide poisoning. A 2-compartment pharmacokinetic model, linked to a sigmoid Emax pharmacodynamic model, was developed to predict the MHb levels after administration of WR 238605 succinate, a primaquine analog to healthy male beagle dogs at 4 daily doses of 6.0 mg/kg (base) orally. Blood plasma drug concns. and MHb levels were detd. over 7 wk. Compartmental and noncompartmental pharmacokinetic and parametric and nonparametric pharmacodynamic analyses were performed. Predicted the peak plasma concns. and MHb levels and the times of their occurrence. The model could be useful for dose and sampling time selection in animal studies and initial **human** clin. testing.

L9 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1991:669673 CAPLUS
DN 115:269673
TI Antimalarial activity of the **8-aminoquinolines**
AU Nodiff, Edward A.; Chatterjee, Sankar; Musallam, Hikmat A.
CS Franklin Res. Cent., Arvin Calspan Corp., Norristown, PA, 19403, USA
SO Progress in Medicinal Chemistry (1991), 28, 1-40
CODEN: PMDCAY; ISSN: 0079-6468
DT Journal; General Review
LA English
AB A review with 216 refs. on the evolution of an extremely promising series of new, broad-spectrum, antimalarial **8-aminoquinolines**. The new drugs are unique in their dual efficacy against the blood and tissue forms of the disease. Structure-activity relations are discussed.

L9 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1990:400536 CAPLUS
DN 113:536
TI Method of inhibiting the activity of **human** immunodeficiency virus (HIV) in vivo
IN Davis, Michael H.
PA USA
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9000055	A1	19900111	WO 1989-US2586	19890619
	W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU				
	RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
				US 1988-213822 A	19880630
	AU 8938529	A1	19900123	AU 1989-38529	19890619
	AU 633499	B2	19930204		
				US 1988-213822 A	19880630

			WO 1989-US2586 A	19890619
EP 422097	A1	19910417	EP 1989-907892	19890619
EP 422097	B1	19940427		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
BR 8907518	A	19910528	BR 1989-7518	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 A	19890619
JP 03505579	T2	19911205	JP 1989-507352	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
AT 104851	E	19940515	AT 1989-907892	19890619
			US 1988-213822 A	19880630
			EP 1989-907892 A	19890619
			WO 1989-US2586 A	19890619
RU 2060032	C1	19960520	RU 1989-4894541	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
RU 2145856	C1	20000227	RU 1994-45248	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
CA 2032748	AA	19920620	CA 1990-2032748	19901219
			US 1988-213822	19880630
US 5153202	A	19921006	US 1991-690314	19910425
			US 1988-213822 B1	19880630
			US 1990-560467 B1	19900727
US 5278173	A	19940111	US 1992-989496	19921210
			US 1988-213811 B1	19880630
			US 1990-560467 B1	19900727
			US 1991-690314 A3	19910425
			US 1991-796244 B1	19911125

PATENT FAMILY INFORMATION:
FAN 2001:312912

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5318979	A	19940607	US 1991-794614	19911115
				US 1988-213822 B2	19880630
				US 1989-418500 B1	19891010
	US 5153202	A	19921006	US 1991-690314	19910425
				US 1988-213822 B1	19880630
				US 1990-560467 B1	19900727
	US 5278173	A	19940111	US 1992-989496	19921210
				US 1988-213811 B1	19880630
				US 1990-560467 B1	19900727
				US 1991-690314 A3	19910425
				US 1991-796244 B1	19911125

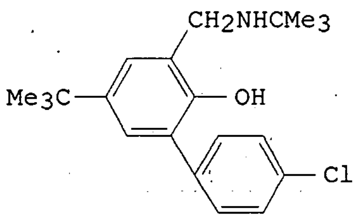
AB Antimalarial drugs of the following classes: alkaloids, 9-aminoacridines, 4-aminoquinolines, **8-aminoquinolines**, biguanides, dihydrofolate reductase inhibitors, sulfones, sulfonamides, mafloquine, halofantrine, hydroxyanilinonaphthyridines, and sesquiterpene lactones, inhibit infection with, or replication of, HIV in vivo.

L9 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1987:131251 CAPLUS
DN 106:131251
TI Effects of antimalarial drugs on interleukin 1-induced cartilage

proteoglycan degradation in vitro
AU Rainsford, K. D.
CS Dep. Pharmacol., Univ. Cambridge, Cambridge, CB2 2QD, UK
SO Journal of Pharmacy and Pharmacology (1986), 38(11), 829-33
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB Previous studies having shown that chloroquine [54-05-7] and hydroxychloroquine [118-42-3] could reduce interleukin 1 (IL-1)-induced cartilage degrdn. in-vitro, the effects of a range of antimalarial drugs on the cartilage proteoglycan degrading actions of porcine leukocyte .alpha.-interleukin 1 were examd. using the std. bovine nasal cartilage culture system. The anti-IL-1 effects in this system were specific to several aminoquinoline and aminoacridine analogs having a side chain with a tertiary amino group similar to that of chloroquine. Aminoquinoline compds. devoid of this side chain and the tertiary amino, as well as pyrimidines or biguanides with antimalarial activity were without effect. Mefloquine [53230-10-7], the most potent of the compds. active against porcine .alpha.-IL-1, was only equipotent with chloroquine and its hydroxy analog against **human** recombinant .alpha.-IL-1. This suggests that there may be subtle differences in the receptors for these drugs and interleukins in bovine cartilage. The results provide further evidence for the specificity and utility of antimalarial drugs in the treatment of chronic inflammatory conditions, esp. in relation to actions on IL-1.

L9 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1986:101744 CAPLUS
DN 104:101744
TI Recent developments in **8-aminoquinoline antimalarials**
AU Bhat, B. K.; Seth, M.; Bhaduri, A. P.
CS Div. Med. Chem., Cent. Drug Res. Inst., Lucknow, 226 001, India
SO Progress in Drug Research (1984), 28, 197-231
CODEN: FAZMAE; ISSN: 0071-786X
DT Journal; General Review
LA English
AB A review, with 152 refs., of the importance of **8-aminoquinoline** derivs. as **antimalarials**. Current progress in **human** and animal studies is described.

L9 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1985:197565 CAPLUS
DN 102:197565
TI The chemotherapy of rodent malaria. XXXVIII. Studies on the activity of three new **antimalarials** (WR 194,965, WR 228,258 and WR 225,448) against rodent and **human** malaria parasites (Plasmodium berghei and P. falciparum)
AU Peters, W.; Irare, S. G.; Ellis, D. S.; Warhurst, D. C.; Robinson, B. L.
CS Dep. Med. Protozool., London Sch. Hyg. Trop. Med., London, WC1E 7HT, UK
SO Annals of Tropical Medicine & Parasitology (1984), 78(6), 567-79
CODEN: ATMPA2; ISSN: 0003-4983
DT Journal
LA English
GI



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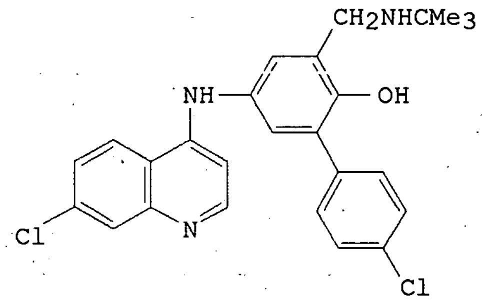

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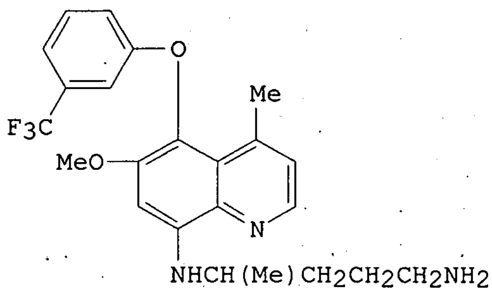
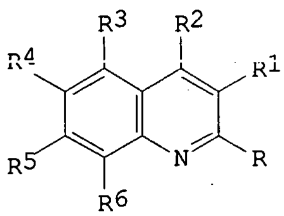


III

AB In addn. to their blood schizontocidal action on P. bergei in vivo, 2 Mannich bases, WR 194,965 (I) [69121-82-0] and WR 228,258 (II) [74129-03-6], are also active against chloroquine-sensitive and chloroquine-resistant lines of P. falciparum in vitro. The response of the lines to each drug differs but shows no correlation in either case with response to chloroquine. The **8-aminoquinoline** WR 225,448 (III) [80065-55-0] is also active against P. falciparum in vitro but at much higher concns. than the Mannich bases. Application of the "chloroquine-induced pigment clumping (CIPC) test" and the study of ultrastructural changes induced in P. berghei in drug-treated mice indicate that WR 194,965 has a mode of action somewhat resembling that of quinine. WR 228,258 in vitro shows a chloroquine-like effect, but not in vivo, suggesting that its mode of action in vivo is different from that of chloroquine. WR 225,448 has no action in the CIPC in vitro and affects primarily mitochondria of the parasites in vivo. It probably acts through a metabolite. Both preerythrocytic and erythrocytic stages of rodent malaria parasites are affected by WR 225,448.

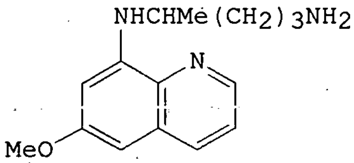
L9 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1984:79470 CAPLUS
DN 100:79470
TI Relationships between chemical structures of **8-aminoquinolines** and their capacities for radical cure of infections with Plasmodium cynomolgi in rhesus monkeys
AU Schmidt, L. H.
CS Inst. Med. Res., Christ Hosp., Cincinnati, OH, 45219, USA
SO Antimicrobial Agents and Chemotherapy (1983), 24(5), 615-52
CODEN: AMACCQ; ISSN: 0066-4804
DT Journal
LA English
GI



I

AB Evaluation of the antimalarial activity of 200 **8-aminoquinolines** I (R = H, Me, OMe, etc.; R1 = H or Me; R2 = H, alkyl, substituted aryl, etc.; R3 = H, OMe, OEtm substituted phenoxy, etc.; R4 = H, Me, OH, etc.; R5 = H, Me, or OMe; R6 = NH2(CH2)nNH, Et2N(CH2)3NH, etc., salts) against sporozoites of P. cynomolgi in rhesus monkeys led to identification of 34 derivs. with activity equal or superior to that of primaquine. Substituents on the quinoline nucleus and side chain that favored or prejudiced curative activity were also characterized. Of the 34 derivs., 19 were as active as primaquine, 9 were twice as active, and 6 were 4 times as active. With respect to nuclear substituents, all were MeO substituted at position 6; 24 had 1 and 10 had 2 addnl. substituents. The addns. with most favorable impact on activity included Me substituents at positions 4 and 2 and alkoxy, F, and a group of 3- or 4-substituted PhO substituents at position 5. With respect to 8-amino substituents, 14 of the 15 derivs. more active than primaquine, and 13 of the 19 as active as primaquine, carried a branched alkyl chain, C4-5 in length, between the 8- and terminal NH2 groups. Proximity of branching to the 8-amino group could be an important determinant of curative activity; however, the effect of such branching was not predictable. All 15 derivs. more active than primaquine and a substantial fraction of those comparable to primaquine in activity have sufficient structural novelty to merit evaluation for tolerability and radical curative activity in **humans**, with reasonable prospects that 1 or more would be better tolerated than primaquine and superior to this drug for cure of P. vivax infections.

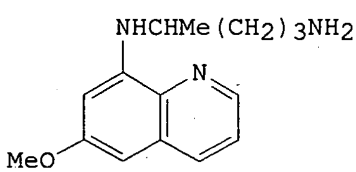
L9 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1982:433041 CAPLUS
DN 97:33041
TI Plasmodium cynomolgi infections in the rhesus monkey. III. Delineation of the potentials of primaquine as a radical curative and prophylactic drug
AU Schmidt, L. H.; Fradkin, Rochelle; Genther, Clara S.; Hughes, Hettie B.
CS Inst. Med. Res., Christ Hosp., Cincinnati, OH, USA
SO American Journal of Tropical Medicine and Hygiene (1982), 31(3, Pt. 2), 666-80
CODEN: AJTHAB; ISSN: 0002-9637
DT Journal
LA English
GI



I

AB The use of primaquine (I) [90-34-6] in **human** volunteers inoculated with sporozites of the Chesson strain of P. vivax and current uses of this **8-aminoquinoline** for curative and preventive purposes were evaluated. Both the curative and prophylactic activities of selected **8-aminoquinolines** in rhesus monkeys infected or challenged with sporozoites of P. cynomolgi and the toxicities of these agents for non-infected monkeys were studied. Preliminary assessments of the curative activities and toxicities of 5 6-methoxyquinolines differing from each other with respect to alkyl substituent in the 8-aminoalkylamino side chain were performed. Primaquine, 1 of these 5 derivs., was the most active and had the best therapeutic index. Expanded evaluations of its curative activity and toxicity, compared with results of earlier appraisals of the activities and toxicities of pamaquine, pentaquine, and isopentaquine, indicated that, with respect to therapeutic indexes, primaquine was superior to these older compds. Evaluations of primaquine for prophylactic activity followed, with emphasis on the influence of the dosage regimen. Apparently, protection against infection with sporozoites could be attained not only by daily dosage throughout the incubation period, but also by 1 or 2 well tolerated doses at appropriate times during this period or by dosage twice weekly for 4 wk after sporozite challenge.

L9 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1977:527289 CAPLUS
DN 87:127289
TI Comparison of the curative antimalarial activities and toxicities of primaquine and its d and l isomers
AU Schmidt, L. H.; Alexander, Sheila; Allen, Linda; Rasco, Jane
CS Kettering-Meyer Lab., South. Res. Inst., Birmingham, AL, USA
SO Antimicrobial Agents and Chemotherapy (1977), 12(1), 51-60
CODEN: AMACCQ; ISSN: 0066-4804
DT Journal
LA English
GI



I

AB The capacities of DL-primaquine (dl-I) [57152-47-3], and the d- [57152-56-4] and l- [57152-58-6] isomers to cure infections with Plasmodium cynomolgi in rhesus monkeys were essentially identical, the

subacute toxicities of the isomers and racemate for this monkey were qual. the same, but l-I was 3 to 5 times as toxic as d-I and at least twice as toxic as I. The acute single-dose toxicities of the isomers for mice were not only qual. different, but the d isomer was at least 4 times as toxic as l-I. Since previous appraisals of curative activity and tolerability of **8-aminoquinolines** in rhesus monkeys have correlated well with appraisals in **human** volunteers, attention was focused on results acquired with these test subjects. The relevant evaluations showed that d-I had a therapeutic index at least twice that of I. If this advantage carries over to man, problems that now complicate routine use of I might be obviated.

```
=> dd l13 fbib hitstr abs total
DD IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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L13 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2002:799142 CAPLUS
DN 137:304334
TI The effects of antimalarial drugs on ventricular repolarization
AU Touze, J.-E.; Heno, P.; Fourcade, L.; Deharo, J.-C.; Thomas, G.; Bohan, S.; Paule, P.; Riviere, P.; Kouassi, E.; Buguet, A.
CS Service de Cardiologie, Hopital d'Instruction des Armees, Marseille, Fr.
SO American Journal of Tropical Medicine and Hygiene (2002), 67(1), 54-60
CODEN: AJTHAB; ISSN: 0002-9637
PB American Society of Tropical Medicine and Hygiene
DT Journal
LA English
AB Cardiotoxicity has become a major concern during treatment with antimalarial drugs. Lengthening of the QTc and severe cardiac arrhythmia have been obsd., particularly after treatment with halofantrine for chloroquine-resistant Plasmodium falciparum malaria. The purpose of this prospective study was to evaluate whether antimalarial agents alter dispersion of the QTc and ventricular repolarization dynamicity. Sixty patients with uncomplicated falciparum malaria were randomly allocated in four groups of 15 patients and treated with quinine, mefloquine, artemether, or halofantrine at recommended doses. Patients in treatment groups were compared with a group including 15 healthy controls with no history of malaria and/or febrile illness within the last month. QTc dispersion was measured on surface electrocardiograms. Repolarization dynamicity was analyzed from Holter recordings, which allow automatic beat-to-beat measurement of QT and RR intervals. Plasma drug concn. was detd. by reversed-phase high-performance liq. chromatog. No change in QTc dispersion was obsd. after treatment with quinine, mefloquine, or artemether. Treatment with halofantrine was followed by a significant increase in QTc dispersion at 9 h (P < 0.0001) and 24 h (P < 0.01). Assessment of QT heart rate variability by QT/RR nychtohemeral regression slope demonstrated no significant difference between the artemether (mean .+-. SEM = 0.170.+-.0.048), mefloquine (0.145.+-.0.044), and the control groups (0.172.+-.0.039). A significant decrease in the Q-eT/RR slope was obsd. in the quinine group compared with the control and artemether groups (0.135.+-.0.057; P < 0.04). With halofantrine, a significant increase in

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     the QT/RR regression slope (0.289.+-.0.118) was obsd. (P < 0.0002).  QTc
     interval, QT dispersion, and QT regression slope were significantly
     correlated with halofantrine and quinine plasma concn.  Mefloquine and
     artemether did not alter ventricular repolarization.  Quinine induced a
     significant decrease in QT/RR slope of the same order of magnitude as
     those previously obsd. with quinidine.  Both QTc dispersion and
     QT/RR slope were significantly modified by halofantrine.  These
     repolarization changes were related to a class-III antiarrhythmic drug
     effect and may explain the occurrence of ventricular arrhythmia and/or
     sudden deaths reported after halofantrine intake.
RE.CNT  35    THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13  ANSWER 2 OF 26  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:778718  CAPLUS
DN   137:289046
TI   Methods and compositions for enhancing pharmaceutical treatments
IN   Newman, Michael J.; Dixon, William Ross
PA   USA
SO   U.S. Pat. Appl. Publ., 47 pp., Cont.-in-part of U.S. Ser. No. 684,293.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   US 2002147197     A1   20021010      US 2002-104549   20020320
                                          US 1999-158322PP 19991008
                                          US 2000-684293 A220001006
PATENT FAMILY INFORMATION:
FAN  2001:283724
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   WO 2001026467     A1   20010419      WO 2000-US27612  20001006
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
            HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
            LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
            SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
            YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
            CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                                          US 1999-158322PP 19991008
     EP 1221847        A1   20020717      EP 2000-968797   20001006
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL
                                          US 1999-158322PP 19991008
                                          WO 2000-US27612W 20001006
     JP 2003511396     T2   20030325      JP 2001-529267   20001006
                                          US 1999-158322PP 19991008
                                          WO 2000-US27612W 20001006
OS   MARPAT 137:289046
AB   Improved methods are provided for therapeutic and/or preventative
     treatment to a mammal in which the mammal is protected against the
     toxicity of active pharmaceutical agents that (i) bind to or are
     substrates for P-gp, (ii) are taxane analogs, and/or (iii) are inhibitors
```

of tubulin disassembly. Addnl. provided are compns. and methods useful for treating cell proliferative disorders. Further provided are methods of increasing the bioavailability of therapeutic and/or preventative treatments in a mammal. Particular embodiments are directed to increasing such bioavailability across the blood-brain barrier.

L13 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2002:95119 CAPLUS
DN 136:379512
TI Inhibition of glutathione S-transferases by antimalarial drugs possible implications for circumventing anticancer drug resistance
AU Mukanganyama, Stanley; Widersten, Mikael; Naik, Yogeshkumar S.; Mannervik, Bengt; Hasler, Julia A.
CS Department of Biochemistry, University of Zimbabwe, Harare, Zimbabwe
SO International Journal of Cancer (2002), 97(5), 700-705
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB A strategy to overcome multidrug resistance in cancer cells involves treatment with a combination of the antineoplastic agent and a chemomodulator that inhibits the activity of the resistance-causing protein. The aim of the authors study was to investigate the effects of antimalarial drugs on **human** recombinant glutathione S-transferase (GSTs) activity in the context of searching for effective and clin. acceptable inhibitors of these enzymes. **Human** recombinant GSTs, heterologously expressed in Escherichia coli were used for inhibition studies. GST A1-1 activity was inhibited by artemisinin with an IC50 of 6 .mu.M, while GST M1-1 was inhibited by **quinidine** and its diastereoisomer quinine with IC50s of 12 .mu.M and 17 .mu.M, resp. GST M3-3 was inhibited by tetracycline only with an IC50 of 47 .mu.M. GST P1-1 was the most susceptible enzyme to inhibition by **antimalarials** with IC50 values of 1, 2, 1, 4, and 13 .mu.M for pyrimethamine, artemisinin, **quinidine**, quinine and tetracycline, resp. The IC50 values obtained for artemisinin, quinine, **quinidine** and tetracycline are below peak plasma concns. obtained during therapy of malaria with these drugs. It seems likely, therefore, that GSTs may be inhibited in vivo at doses normally used in clin. practice. Using the substrate ethacrynic acid, a diuretic drug also used as a modulator to overcome drug resistance in tumor cells, GST P1-1 activity was inhibited by tetracycline, quinine, pyrimethamine and **quinidine** with IC50 values of 18, 27, 45 and 70 .mu.M, resp. The ubiquitous expression of GSTs in different malignancies suggests that the addn. of nontoxic reversing agents such as **antimalarials** could enhance the efficacy of a variety of alkylating agents.
RE.CNT 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2001:869348 CAPLUS
DN 136:63532
TI Improved RP-HPLC determination of quinine in plasma and whole blood stored on filter paper
AU Kolawole, J. A.; Mustapha, A.
CS Department of Pharmaceutical Chemistry, University of Jos, Jos, Nigeria
SO Biopharmaceutics & Drug Disposition (2000), 21(9), 345-352
CODEN: BDDID8; ISSN: 0142-2782

PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Anal. of quinine in blood plasma and whole blood samples dried on filter paper is described. Sample prepn. involves liq. extn. of plasma and whole blood from the filter paper and subsequent solid-phase extn. using C8 Bond Elut cartridges. A reverse-phase liq. chromatog. system with UV detection and fluorescence detection was used. The anal. characteristics of the method are reported, with a quantification limit of 0.1 .mu.g mL-1 and within an assay coeff. of variation of 5.6-8.4% in plasma and 6.5-12% in whole blood. Representative chromatograms are shown as a function of time for samples from **human** subjects after ingestion of a single 400-mg dose of quinine sulfate. **Quinidine,** dihydroquinine and metabolites are well sepd. from quinine with a resoln. of above 1 (Rs > 1).
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2001:711673 CAPLUS
DN 136:63622
TI Interactions of the antimalarial drug mefloquine with the **human** cardiac potassium channels KvLQT1/minK and HERG
AU Kang, Jiesheng; Chen, Xiao-Liang; Wang, Lin; Rampe, David
CS Drug Safety Evaluation, Aventis Pharmaceuticals, Inc., Bridgewater, NJ, USA
SO Journal of Pharmacology and Experimental Therapeutics (2001), 299(1), 290-296
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Mefloquine is a quinoline antimalarial drug that is structurally related to the antiarrhythmic agent **quinidine**. Mefloquine is widely used in both the treatment and prophylaxis of Plasmodium falciparum malaria. Mefloquine can prolong cardiac repolarization, esp. when coadministered with halofantrine, an antagonist of the **human** ether-a-go-go-related gene (HERG) cardiac K+ channel. For these reasons we examd. the effects of mefloquine on the slow delayed rectifier K+ channel (KvQT1/minK) and HERG, the K+ channels that underlie the slow (IKs) and rapid (IKr) components of repolarization in the **human** myocardium, resp. Using patch-clamp electrophysiol. we found that mefloquine inhibited KvLQT1/minK channel currents with an IC50 value of approx. 1 .mu.M. Mefloquine slowed the activation rate of KvLQT1/minK and more block was evident at lower membrane potentials compared with higher ones. When channels were held in the closed state during drug application, block was immediate and complete with the first depolarizing step. HERG channel currents were about 6-fold less sensitive to block by mefloquine (IC50 = 5.6 .mu.M). Block of HERG displayed a pos. voltage dependence with maximal inhibition obtained at more depolarized potentials. In contrast to structurally related drugs such as **quinidine,** mefloquine is a more effective antagonist of KvLQT1/minK compared with HERG. Block of KvLQT1/minK by mefloquine may involve an interaction with the closed state of the channel. Inhibition by mefloquine of KvLQT1/minK in the **human** heart may in part explain the synergistic prolongation of QT interval obsd. when this drug is coadministered with the HERG antagonist halofantrine.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2001:509718 CAPLUS
DN 135:282575
TI Pharmacokinetic interactions of antimalarial agents
AU Giao, Phan Trong; de Vries, Peter J.
CS Division of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center, Amsterdam, Neth.
SO Clinical Pharmacokinetics (2001), 40(5), 343-373
CODEN: CPKNDH; ISSN: 0312-5963
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review with refs. Combination of antimalarial agents has been introduced as a response to widespread drug resistance. The higher no. of mutations required to express complete resistance against combinations may retard the further development of resistance. Combination of drugs, esp. with the artemisinin drugs, may also offer complete and rapid eradication of the parasite load in symptomatic patients and thus reduce the chance of survival of resistant strains. The advantages of combination therapy should be balanced against the increased chance of drug interactions. During the last decade, much of the pharmacokinetics and metabolic pathways of antimalarial drugs have been elucidated, including the role of the cytochrome P 450 (CYP) enzyme complex. Change in protein binding is not a significant cause of interactions between antimalarial agents. CYP3A4 and CYP2C19 are frequently involved in the metab. of antimalarial agents. **Quinidine** is a potent inhibitor of CYP2D6, but it appears that this enzyme does not mediate the metab. of any other antimalarial agent. The new combinations proguanil-atovaquone and chlorproguanil-dapsone do not show significant interactions. CYP2B6 and CYP3A4 are involved in the metab. of artemisinin and derivs., but further studies may reveal involvement of more enzymes. Artemisinin may induce CYP2C19. Several artemisinin drugs suffer from autoinduction of the first-pass effect, resulting in a decline of bioavailability after repeated doses. The mechanism of this effect is not yet clear, but induction by other agents cannot be excluded. The combination of artemisinin drugs with mefloquine and the fixed combination artemether-lumefantrine have been studied widely, and no significant drug interactions have been found. The artemisinin drugs will be used at an increasing rate, particularly in combination with other agents. Although clin. studies have so far not shown any significant interactions, drug interactions should be given appropriate attention when other combinations are used.
RE.CNT 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2001:317936 CAPLUS
DN 136:193666
TI Oral quinine pharmacokinetics and dietary salt intake
AU Newton, Paul; Simpson, Andrew; Wanwimolruk, Sompon; Maliakal, Pius; Villegas, Leopoldo; Kuypers, Daniel; White, Nicholas J.
CS Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
SO European Journal of Clinical Pharmacology (2001), 57(2), 111-113
CODEN: EJCPAS; ISSN: 0031-6970

PB Springer-Verlag
DT Journal
LA English
AB Objectives: The objective was to det. whether or not dietary salt intake affects the relative bioavailability of oral quinine. Salt intake was shown to alter **quinidine** bioavailability. Methods: The pharmacokinetic properties of oral quinine sulfate (600 mg salt) were investigated in 7 healthy Caucasian volunteers, in a randomized, cross-over study, on low- and high-salt diets. Plasma quinine concns. were measured by high-performance liq. chromatog. (HPLC) and the 24-h urinary sodium excretion was assayed. Results: Although the 24-h urine sodium excretion was significantly higher when the volunteers were on a high-salt diet, there were no significant differences in quinine AUC0-.infin.,tmax, andCmax after the 2 diets. The median (range) quinine elimination half-life was significantly shorter after a high-salt diet [8.5 (4.3-10.2) h] than after a low-salt diet [10.0 (7.6-14.8) h] (P=0.04). Conclusion: Dietary salt does not affect the relative oral bioavailability of quinine sulfate.
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2001:152494 CAPLUS
DN 134:206558
TI Malaria GPI anchors as vaccines anti-parasitic drugs and for use in diagnostics
IN Gowda, D. Channe; Davidson, Eugene A.
PA Georgetown University, USA
SO PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001013923	A1	20010301	WO 2000-US22876	20000818

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 1999-149716PP 19990820

OS MARPAT 134:206558
AB This invention relates to compns. and methods for treating or preventing malaria in host organisms, esp. malaria in **humans**. The methods for treating or preventing malaria involve inhibiting or blocking the action or pathol. mediated by a Plasmodium glycosylphosphatidylinositol (GPI). The invention also provides a kit for diagnosing whether a subject has been exposed to malaria.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 2000:366042 CAPLUS
DN 133:785
TI Use of phosphonformic acid derivatives for the prevention and treatment of infections and for fungicides, bactericides, and herbicides in plants
IN Jomaa, Hassan
PA Germany

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SO    Ger. Offen., 10 pp.
      CODEN: GWXXBX
DT    Patent
LA    German
FAN.CNT 1
      PATENT NO.         KIND  DATE            APPLICATION NO.   DATE
      ---------------    ----  --------        ---------------   --------
PI    DE 19854402         A1   20000531        DE 1998-19854402  19981125
      WO 2000030625       A2   20000602        WO 1999-EP8965    19991120
      WO 2000030625       A3   20001005
          W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
              CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
              IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
              MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
              SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
              BY, KG, KZ, MD, RU, TJ, TM
          RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
              DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
              CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                                               DE 1998-19854402A 19981125
      BR 9915639          A    20010807        BR 1999-15639     19991120
                                               DE 1998-19854402A 19981125
                                               WO 1999-EP8965 W  19991120
      EP 1131075          A2   20010912        EP 1999-958099    19991120
          R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
              IE, SI, LT, LV, FI, RO
                                               DE 1998-19854402A 19981125
                                               WO 1999-EP8965 W  19991120
      JP 2002530326       T2   20020917        JP 2000-583508    19991120
                                               DE 1998-19854402A 19981125
                                               WO 1999-EP8965 W  19991120
      NO 2001002541       A    20010724        NO 2001-2541      20010523
                                               DE 1998-19854402A 19981125
                                               WO 1999-EP8965 W  19991120
OS    MARPAT 133:785
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AB Phosphonformic acid derivs. (Markush included) are used for the prevention and treatment of infectious conditions in **humans** and animals which are caused by bacteria, fungi, or parasites, as well as for fungicides, bactericides, and herbicides in plants.

L13 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1999:302432 CAPLUS
DN 131:97019
TI Effect of selected antimalarial drugs and inhibitors of cytochrome P-450 3A4 on halofantrine metabolism by **human** liver microsomes
AU Baune, B.; Furlan, V.; Taburet, A. M.; Farinotti, R.
CS Faculte de pharmacie, Departement de Pharmacie Clinique, Chatenay-Malabry, 92290, Fr.
SO Drug Metabolism and Disposition (1999), 27(5), 565-568
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Halofantrine (HF) is used in the treatment of uncomplicated multidrug-resistant Plasmodium falciparum malaria. Severe cardiotoxicity has been reported to be correlated with high plasma concns. of HF but not with that of its metabolite N-debutylhalofantrine. The aim of this study

was to investigate the effects of other antimalarial drugs and of ketoconazole, a typical cytochrome P 450 3A4 inhibitor, on HF metab. by **human** liver microsomes. Antimalarial drug inhibitory effects were ranked as follows: primaquine > proguanil > mefloquine > quinine > **quinidine** > artemether > amodiaquine. Artemisinin, doxycycline, sulfadoxine, and pyrimethamine showed little or no inhibition of HF metab. Mefloquine, quinine, **quinidine**, and ketoconazole used at maximal plasma concns. inhibited N-debutylhalofantrine formation noncompetitively with K1 values of 70 .mu.M, 49 .mu.M, 62 .mu.M, and 0.05 .mu.M resulting in 7%, 49%, 26%, and 99% inhibition, resp., in HF metab. In conclusion, we showed that quinine and **quinidine** coadministered with HF might inhibit its metab. resulting in the potentiation of HF-induced cardiotoxicity in patients. This requires a close monitoring of ECG. For the same reasons, the concomitant administration of HF and ketoconazole must be avoided. By contrast, none of the other **antimalarials** studied inhibited HF metab. and, by extrapolation, cytochrome P 450 3A4 activity.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2003 ACS

AN 1998:271658 CAPLUS

DN 129:91084

TI Identification of Saccharomyces cerevisiae genes conferring resistance to quinoline ring-containing antimalarial drugs

AU Delling, Ulrike; Raymond, Martine; Schurr, Erwin

CS McGill Centre for the Study of Host Resistance, Departments of Medicine and Biochemistry, Montreal General Hospital Research Institute, McGill University, Montreal, QC, H3G 1A4, Can.

SO Antimicrobial Agents and Chemotherapy (1998), 42(5), 1034-1041
CODEN: AMACCQ; ISSN: 0066-4804

PB American Society for Microbiology

DT Journal

LA English

AB To identify genes that can confer resistance to antimalarial drugs in yeast, the authors transformed the **quinidine** sensitive strain CYX247-9A of Saccharomyces cerevisiae with a yeast genomic library and selected for transformants that grow in the presence of elevated levels of antimalarial drugs. Plasmids were rescued from such clones and were analyzed for the presence of individual open reading frames that can confer drug resistance. Using **quinidine** as the selective drug, the authors were able to identify three genes that can cause resistance to antimalarial drugs. Overexpression of the yeast genes CIN5 (a member of the family of bZIP transcription factors), STI1 (a Hsp90 cochaperone), and YOR273c (a member of the major facilitator superfamily of transmembrane transporters) conferred 3.9-, 7.0-, and 4.3-fold resistance to **quinidine**, resp., over that of control yeast. Cross-resistance assays detd. that STI1 also conferred resistance to mefloquine (3.4-fold), while CIN5 also conferred resistance to mefloquine (9.6-fold) and chloroquine (5.4-fold). Using mefloquine as the selective drug, the authors detd. that overexpression of YBR233w, a member of the hnRNPK family of nuclear RNA binding proteins, conferred resistance to mefloquine (13.5-fold). Expression of the **human** hnRNPK homolog of YBR233w in S. cerevisiae also conferred mefloquine resistance, suggesting that homologs of the identified resistance genes may perform similar functions in species other than yeast. These expts. have identified heretofore unknown pathways of resistance to quinoline ring-contg. antimalarial drugs

in S. cerevisiae.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1998:241711 CAPLUS
DN 129:12324
TI Metabolism of .beta.-arteether to dihydroqinghaosu by **human** liver microsomes and recombinant cytochrome P450
AU Grace, James M.; Aguilar, Antonio J.; Trotman, Kimberly M.; Brewer, Thomas G.
CS Department of Pharmacology, Walter Reed Army Institute of Research, Washington, DC, 20307-5100, USA
SO Drug Metabolism and Disposition (1998), 26(4), 313-317
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB .beta.-Arteether (AE) is an endoperoxide sesquiterpene lactone deriv. currently being developed for the treatment of severe, complicated malaria caused by multidrug-resistant Plasmodium falciparum. Studies were undertaken to det. which form(s) of **human** cytochrome P 450 catalyze the conversion of .beta.-arteether to its deethylated metabolite, dihydroqinghaosu (DQHS), itself a potent antimalarial compd. In **human** liver microsomes, AE was metabolized to DQHS with a Km of 53.7 .+-. 29.5 .mu.M and a Vmax of 1.64 .+-. 1.78 nmol DQHS/min/mg protein. AE biotransformation to DQHS was inhibited by ketoconazole and troleandomycin. Ketoconazole was a competitive inhibitor, with an apparent Ki of 0.33 .+-. 0.11 .mu.M. Because AE is being developed for patients who fail primary treatment, it is possible that AE may be involved in life-threatening drug-drug interactions, such as the assocd. cardiotoxicity of mefloquine and **quinidine**. Coincubation of AE with other **antimalarials** showed mefloquine and **quinidine** to be competitive inhibitors with a mean Ki of 41 and 111 .mu.M, resp. Metab. of AE using **human** recombinant P450s provided evidence that cytochrome P450s 2B6, 3A4, and 3A5 were the primary isoenzymes responsible for its deethylation. CYP3A4 metabolized AE to dihydroqinghaosu at a rate approx. 10 times that of CYP2B6 and .apprx.4.5-fold greater than that of CYP3A5. These results demonstrate that CYP3A4 is the primary isoenzyme involved in the metab. of AE to its active metabolite, DQHS, with secondary contributions by CYP2B6 and -3A5.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1998:147346 CAPLUS
DN 128:213381
TI Compositions and methods for treating infections using analogs of indolicidin
IN Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
PA Micrologix Biotech, Inc., Can.; Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA English

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FAN.CNT 3
     PATENT NO.        KIND  DATE            APPLICATION NO.   DATE
     ---------------   ----  --------        ---------------   --------
PI   WO 9807745         A2   19980226        WO 1997-US14779   19970821
     WO 9807745         A3   19980709
         W:  AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,
             EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN,
             YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
     AU 9743279         A1   19980306        AU 1997-43279     19970821
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
                                             WO 1997-US14779W 19970821
     EP 925308          A2   19990630        EP 1997-941352    19970821
     EP 925308          B1   20020605
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
                                             WO 1997-US14779W 19970821
     JP 2001500477      T2   20010116        JP 1998-510994    19970821
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
                                             WO 1997-US14779W 19970821
     EP 1174439         A2   20020123        EP 2001-119148    19970821
     EP 1174439         A3   20030326
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
                                             EP 1997-941352 A319970821
     AT 218579          E    20020615        AT 1997-941352    19970821
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
                                             WO 1997-US14779W 19970821
     ES 2178000         T3   20021216        ES 1997-941352    19970821
                                             US 1996-24754P P 19960821
                                             US 1997-34949P P 19970113
PATENT FAMILY INFORMATION:
FAN  1998:621235
     PATENT NO.        KIND  DATE            APPLICATION NO.   DATE
     ---------------   ----  --------        ---------------   --------
PI   WO 9840401         A2   19980917        WO 1998-CA190     19980310
     WO 9840401         A3   19981217
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
             UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
             FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
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GA, GN, ML, MR, NE, SN, TD, TG

				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
	US 6180604	B1	20010130	US 1997-915314	19970820
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
	AU 9866047	A1	19980929	AU 1998-66047	19980310
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	EP 966481	A2	19991229	EP 1998-907779	19980310
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	JP 2002544759	T2	20021224	JP 1998-538997	19980310
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310

FAN 2002:221202

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002035061	A1	20020321	US 1998-30619	19980225
	US 6503881	B2	20030107		
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				US 1997-40649P P	19970310
				US 1997-915314 A2	19970820
				US 1997-60099P P	19970926
	US 6180604	B1	20010130	US 1997-915314	19970820
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
	EP 1174439	A2	20020123	EP 2001-119148	19970821
	EP 1174439	A3	20030326		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				EP 1997-941352 A3	19970821
	AU 9866047	A1	19980929	AU 1998-66047	19980310
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	EP 966481	A2	19991229	EP 1998-907779	19980310
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				US 1997-40649P P	19970310

			US 1997-915314	A 19970820
			US 1997-60099P	P 19970926
			US 1998-30619	A 19980225
			WO 1998-CA190	W 19980310
JP 2002544759	T2	20021224	JP 1998-538997	19980310
			US 1997-40649P	P 19970310
			US 1997-915314	A 19970820
			US 1997-60099P	P 19970926
			US 1998-30619	A 19980225
			WO 1998-CA190	W 19980310
US 6538106	B1	20030325	US 2000-667486	20000922
			US 1996-24754P	P 19960821
			US 1997-34949P	P 19970113
			US 1997-915314	A119970820

OS MARPAT 128:213381
AB Compns. and methods for treating infections, esp. bacterial infections, are provided. Indolicidin peptide analogs contg. at least two basic amino acids are prepd. The analogs are administered as modified peptides, preferably contg. photo-oxidized solubilizer.

L13 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1997:778099 CAPLUS
DN 128:84153
TI Is halofantrine still advisable in malaria attacks?
AU Touze, J. E.; Fourcade, L.; Peyron, F.; Heno, P.; Deharo, J. C.
CS Institut de Medecine Tropicale du Service de Sante des Armees, Marseille, 13998, Fr.
SO Annals of Tropical Medicine and Parasitology (1997), 91(7), 867-873
CODEN: ATMPA2; ISSN: 0003-4983
PB Carfax Publishing Ltd.
DT Journal
LA English
AB Halofantrine is an antimalarial drug which is widely prescribed for the treatment of infections with chloroquine-resistant strains of Plasmodium falciparum. Chem., it is a phenanthrene methanol, belonging to the aryl-amino-alc. family. It has recently been recognized that this drug may induce rare but serious, cardiotoxic effects, including lengthening of the QTc interval, "torsade de pointes" and induction of late ventricular potentials. These events are thought to be related to a **quinidine** -like action of the drug. In addn., severe hemolytic accidents have been reported, mimicking blackwater fever and indicating an immunol. process. As a result of these side-effects, new guidelines for prescription and more cautious use of halofantrine, particularly as a stand-by treatment for febrile access among travelers, are required.

L13 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1997:752413 CAPLUS
DN 128:57090
TI Metabolic interactions of selected antimalarial and non-antimalarial drugs with the major pathway (3-hydroxylation) of quinine in **human** liver microsomes
AU Zhao, Xue-Jun; Ishizaki, Takashi
CS Department of Clinical Pharmacology, International Medical Center of Japan, Research Institute, Tokyo, 162, Japan
SO British Journal of Clinical Pharmacology (1997), 44(5), 505-511
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.

DT Journal
LA English
AB Nine antimalarial (plus two metabolites of proguanil) and twelve non-antimalarial drugs were tested for their possible interaction with CYP3A4-catalyzed 3-hydroxylation of quinine by **human** liver microsomes in vitro. 3-Hydroxyquinine was assayed in the incubation mixt. by an h.p.l.c. method using fluorometric detection. The resp. IC50 values were estd. for the twenty-one drugs and two metabolites of proguanil tested herein. Thirteen drugs exhibited an inhibitory effect on the 3-hydroxylation of quinine. According to the resp. mean IC50 values, the inhibitory rank order of the drugs was: ketoconazole > troleandomycin (TAO, with preincubation) > doxycycline > omeprazole > primaquine > tetracycline = TAO (without preincubation) > nifedipine > erythromycin > verapamil > cimetidine > diltiazem > oleandomycin > hydralazine. Other drugs or metabolites showed little or no inhibition of quinine metab. (mean IC50 > 200 or 500 .mu.M). Among the antimalarial drugs, doxycycline showed relatively potent inhibition of quinine 3-hydroxylation with a mean IC50 value of 17 .mu.M, followed by primaquine and tetracycline, with mean IC50 values of 20 and 29 .mu.M, resp. When the plasma/serum concns. possibly attained after their usual therapeutic doses were taken into account, tetracycline, doxycycline, omeprazole, ketoconazole, nifedipine, TAO and erythromycin are likely to be inhibitors of quinine metab. in patients when the drugs are co-administrated with quinine.

L13 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1997:408377 CAPLUS
DN 127:44278
TI Chemotherapy of cerebral malaria: current recommendations for treatment and prophylaxis
AU Wilairatana, Polrat; Looareesuwan, Sornchai; Walsh, Douglas S.
CS Division of Critical Care for Tropical Diseases, Hospital for Tropical Disease, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
SO CNS Drugs (1997), 7(5), 366-380
CODEN: CNDREF; ISSN: 1172-7047
PB Adis
DT Journal; General Review
LA English
AB A review with .apprx.116 refs. Cerebral malaria is a potentially fatal manifestation of "severe" malaria caused by Plasmodium falciparum. It is an esp. important problem for African children because it is a major cause of death due to malaria. The pathophysiol. of cerebral disease is characterized by complex host-parasite interactions. Optimal management of cerebral malaria is also complex, requiring accurate diagnosis, prompt treatment with one of the few remaining effective antimalarial drugs, and recognition that cerebral disease is frequently accompanied by other major organ dysfunction requiring addnl. care. Three classes of antimalarial drugs are useful for cerebral malaria: the 4-aminoquinolines (chloroquine), the cinchona alkaloids (quinine, **quinidine**) and the artemisinin compds. (artesunate, artemether). Chloroquine is the drug of choice in the few areas of the world where the falciparum parasite remains sensitive. In most malarious regions, however, the cinchona alkaloids and the artemisinin compds. are the only remaining options. In some areas of Southeast Asia, resistance to quinine is established, further limiting treatment options and raising concerns for the future. Artemisinin compds., an exciting new class of antimalarial drugs developed in China, are the most rapidly acting of all the antimalarial drugs, with

little known toxicity. Despite new insight into the pathogenesis of cerebral malaria and powerful antiparasitic therapies, the mortality rates in patients with this disease have remained stable over many years and are unacceptably high, ranging from 10 to 50%. Thus, malaria remains a tremendous public health problem that requires continued efforts to better understand pathophysiol. and develop more effective therapies. The best way to prevent cerebral malaria is to prevent infection with P. falciparum. Most approaches are based on a chemoprophylactic regimen in combination with other measures such as repellents and insect screens. Even though no regimen is completely effective, chemoprophylaxis may reduce the subsequent risk of cerebral malaria if a "breakthrough" falciparum infection is acquired. Addnl., early diagnosis and prompt treatment of individuals with uncomplicated falciparum malaria may diminish the risk of cerebral malaria.

L13 ANSWER 17 OF 26 CAPLUS
AN 1995:971826 CAPLUS
DN 124:75473
TI An investigation of the interaction between halofantrine, CYP2D6 and CYP3A4: Studies with **human** liver microsomes and heterologous enzyme expression systems
AU Halliday, Rachel C.; Jones, Barry C.; Smith, Dennis A.; Kitteringham, Neil R.; Park, B. Kevin
CS Department Pharmacology and Therapeutics, University Liverpool, Liverpool, L69 3BX, UK
SO British Journal of Clinical Pharmacology (1995), 40(4), 369-78
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell
DT Journal
LA English
AB The authors have assessed the interaction of the antimalarial halofantrine with cytochrome P 450 (CYP) enzymes in vitro, with the use of microsomes from **human** liver and recombinant cell lines. Rac-halofantrine was a potent inhibitor (IC50 = 1.06 .mu.M, Ki = 4.3 .mu.M) of the 1-hydroxylation of bufuralol, a marker for CYP2D6 activity. Of a group of structurally related **antimalarials** tested, only **quinidine** (IC50 = 0.04 .mu.M) was more potent. Microsomes prepd. from recombinant CYP2D6 and CYP3A4 cell lines were shown to catalyze halofantrine N-debutylation. The metab. of halofantrine to its N-desbutyl metabolite by **human** liver microsomes showed no correlation with CYP2D6 genotypic or phenotypic status and there was no consistent inhibition by **quinidine**. The rate of halofantrine metab. showed a significant correlation with both CYP3A4 protein levels (r = 0.88) and the rate of felodipine metab. (r = 0.86), a marker substrate for CYP3A4 activity. Inhibition studies showed that ketoconazole is a potent inhibitor of halofantrine metab. (IC50 = 1.57 .mu.M). In conclusion, the authors have demonstrated that halofantrine is a potent inhibitor of CYP2D6 in vitro and can also be metabolized by the enzyme. However, in **human** liver microsomes it appears to be metabolized largely by CYP3A4.

L13 ANSWER 18 OF 26 CAPLUS
AN 1995:225892 CAPLUS
DN 122:408
TI Quinine and **quinidine** inhibit and reveal heterogeneity of K-Cl cotransport in low K sheep erythrocytes
AU Adragna, N. C.; Lauf, P. K.

CS School Medicine, Wright State University, Dayton, OH, 45401-0927, USA
SO Journal of Membrane Biology (1994), 142(2), 195-207
CODEN: JMBBBO; ISSN: 0022-2631
PB Springer
DT Journal
LA English
AB Low K (LK) sheep red blood cells (SRBCs) serve as a model to study K-Cl cotransport which plays an important role in cellular dehydration in **human** erythrocytes homozygous for Hb S. Cinchona bark derivs., such as quinine (Q) and **quinidine** (QD), are effectively used in the treatment of malaria. In the present study, we investigated n LK SRBCs, the effect of various concns. of Q and QD on Cl-dependent K efflux and Rb influx (K(Rb)-Cl flux), activated by either swelling in hyposmotic media, thiol alkylation with N-ethylmaleimide (NEM), or by cellular Mg (Mgi) removal through A23187 in the presence of external chelators. K efflux or Rb influx were detd. in Cl and NO3 medium and K(Rb)-Cl flux was defined as the Cl-dependent (Cl minus NO3) component. K(Rb)-Cl flux stimulated by all three interventions was inhibited by both Q and QD in a dose-dependent manner. Max. inhibition of K(Rb)-Cl flux occurred at Q and QD concns. .gtoreq.1 mM. The inhibitory effect of Q was manifested n Cl, but not in NO3, whereas QD reduced K and Rb fluxes both in Cl and NO3 media. The mean 50% inhibitory concn. (IC50) of Q and QD to inhibit K(Rb)-Cl flux varied between 0.23 and 2.24 mM. From detns. of the percentages of inhibition of the different components of K and Rb fluxes, we found that SRBCs possess a Cl-dependent QD-sensitive and a Cl-dependent QD-insensitive K efflux and Rb influx. These two components vary in magnitude depending on the manipulation and directional flux, but in av. they are about 50% of the total Cl-dependent flux. This study raises the possibility that, in SRBCs, the Cl-dependent K(Rb) fluxes are heterogeneous.

L13 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1993:400186 CAPLUS
DN 119:186
TI Determination of quinine in serum, plasma, red blood cells and whole blood in healthy and Plasmodium falciparum malaria cases by high-performance liquid chromatography
AU Dua, Virendra K.; Sarin, Reema; Prakash, Anil
CS Malar. Res. Cent., BHEL, Hardwar, 249403, India
SO Journal of Chromatography, Biomedical Applications (1993), 614(1), 87-93
CODEN: JCBADL; ISSN: 0378-4347
DT Journal
LA English
AB A normal-phase high-performance liq. chromatog. method using dichloromethane-methanol-1 M perchloric acid (100:9:0.4, vol./vol.) at a flow-rate of 0.8 mL/min on a Zorbax-Sil column with fluorescence detection has been developed for the sepn. of quinine and **quinidine** from other **antimalarials**. Within-day and day-to-day coeffs. of variation averaged 0.74 and 7.556%, resp. The extn. recovery of quinine for plasma, serum, red blood cells and whole blood (filter paper) was 88.13, 87.12, 78.0 and 77.5%, resp. The method is capable of sepg. quinine from dihydroqunine, a compd. usually found as an impurity in authentic quinine samples. The method has been used for the detn. of quinine in plasma, serum, red blood cells and whole blood (filter paper) of six healthy and twenty P. falciparum malaria cases. The av. quinine concn. in P. falciparum malaria cases was three to four times higher than that in healthy volunteers. Quinine was absorbed much less in red blood

cells than in plasma or serum.

L13 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1990:452100 CAPLUS
DN 113:52100
TI Inhibition of metoprolol metabolism by chloroquine and other antimalarial drugs
AU Lancaster, D. L.; Adio, R. A.; Tai, K. K.; Simooya, O. O.; Broadhead, G. D.; Tucker, G. T.; Lennard, M. S.
CS Univ. Dep. Med. Pharmacol., R. Hallamshire Hosp., Sheffield, S10 2JF, UK
SO Journal of Pharmacy and Pharmacology (1990), 42(4), 267-71
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB The ability of a series of antimalarial drug to impair the metab. of metoprolol was studied in rats and man. Chloroquinine was a potent inhibitor in rat liver microsomes (Ki value for metoprolol .alpha.-hydroxylation = 0.18 .mu.M and for O-demethylation = 0.36 .mu.M). The other antimalarial drugs also inhibited metoprolol oxidn. Quinine was similar to chloroquine in potency, while **quinidine,** primaquine and mefloquine were slightly less potent. Chloroquine also inhibited metoprolol oxidn. in **human** liver microsomes, although it was about 2 orders of magnitude less potent than in the rat and the extent of impairment varied greatly between individual livers. I.p. administration of chloroquine to anesthetized rats decreased the clearance of metoprolol (40 mg tartrate salt kg-1 i.p.) to 54, 34, 20 and 26% of the control value at doses of 2.5, 4.0, 25 and 40 mg kg-1, resp. Apparently, antimalarial treatment might have contributed to a previously reported difference in the metabolic pattern of metoprolol between Caucasians and Nigerians.

L13 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1990:400536 CAPLUS
DN 113:536
TI Method of inhibiting the activity of **human** immunodeficiency virus (HIV) in vivo
IN Davis, Michael H.
PA USA
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9000055	A1	19900111	WO 1989-US2586	19890619
	W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU				
	RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
				US 1988-213822 A	19880630
	AU 8938529	A1	19900123	AU 1989-38529	19890619
	AU 633499	B2	19930204		
				US 1988-213822 A	19880630
				WO 1989-US2586 A	19890619
	EP 422097	A1	19910417	EP 1989-907892	19890619
	EP 422097	B1	19940427		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				

			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
BR 8907518	A	19910528	BR 1989-7518	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 A	19890619
JP 03505579	T2	19911205	JP 1989-507352	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
AT 104851	E	19940515	AT 1989-907892	19890619
			US 1988-213822 A	19880630
			EP 1989-907892 A	19890619
			WO 1989-US2586 A	19890619
RU 2060032	C1	19960520	RU 1989-4894541	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
RU 2145856	C1	20000227	RU 1994-45248	19890619
			US 1988-213822 A	19880630
			WO 1989-US2586 W	19890619
CA 2032748	AA	19920620	CA 1990-2032748	19901219
			US 1988-213822	19880630
US 5153202	A	19921006	US 1991-690314	19910425
			US 1988-213822	B119880630
			US 1990-560467	B119900727
US 5278173	A	19940111	US 1992-989496	19921210
			US 1988-213811	B119880630
			US 1990-560467	B119900727
			US 1991-690314	A319910425
			US 1991-796244	B119911125

PATENT FAMILY INFORMATION:
FAN 2001:312912

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5318979	A	19940607	US 1991-794614	19911115
				US 1988-213822	B219880630
				US 1989-418500	B119891010
	US 5153202	A	19921006	US 1991-690314	19910425
				US 1988-213822	B119880630
				US 1990-560467	B119900727
	US 5278173	A	19940111	US 1992-989496	19921210
				US 1988-213811	B119880630
				US 1990-560467	B119900727
				US 1991-690314	A319910425
				US 1991-796244	B119911125

AB Antimalarial drugs of the following classes: alkaloids, 9-aminoacridines, 4-aminoquinolines, 8-aminoquinolines, biguanides, dihydrofolate reductase inhibitors, sulfones, sulfonamides, mafloquine, halofantrine, hydroxyanilinonaphthyridines, and sesquiterpene lactones, inhibit infection with, or replication of, HIV in vivo.

L13 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1989:279 CAPLUS
DN 110:279
TI Inhibition of tolbutamide metabolism by antimalarial drugs
AU Karbwang, Juntra; Back, D. J.; Bunnag, Danai; Breckenridge, A. M.
CS Fac. Trop. Med., Mahidol Univ., Bangkok, Thailand
SO Southeast Asian Journal of Tropical Medicine and Public Health (1988), 19(2), 235-41

CODEN: SJTMAK; ISSN: 0125-1562
DT Journal
LA English
AB The effects of mefloquine (MQ), the combination of MQ with sulfadoxine and pyrimethamine (MSP), sulfadoxine (S), pyrimethamine (P), quinine (Q) and **quinidine** (Qd) on in vitro hepatic drug metab. has been studied using tolbutamide as a substrate. The hydroxylation of tolbutamide was detd. in the presence of variable concns. of each compd. Tolbutamide hyroxylase activity in control microsomes was 0.20 nmole/min/mg microsomal protein at a substrate concn. of 150 .mu.M. All compds. studied inhibited tolbutamide metab. as shown by a decrease in 4-hydroxytolbutamide formation. The order of potency of the inhibitors was MSP > S > MQ > Q > Qd > P. MQ, MSP, S, Q, and Qd were examd. in detail for the type of inhibition. MQ and Qd were noncompetitive inhibitors, whereas MSP and S were competitive inhibitors and Q was an uncompetitive inhibitor of tolbutamide 4-hydroxylation. These data provide more information on the inhibitory potential of some antimalarial drugs on microsomal enzymes in **human** liver. S has been shown to be a potent inhibitor in vitro and this finding possibly explains the longer half-life and mean residence time of MQ when coadministered with S in healthy volunteers.

L13 ANSWER 23 OF 26 CAPLUS
AN 1987:131251 CAPLUS
DN 106:131251
TI Effects of antimalarial drugs on interleukin 1-induced cartilage proteoglycan degradation in vitro
AU Rainsford, K. D.
CS Dep. Pharmacol., Univ. Cambridge, Cambridge, CB2 2QD, UK
SO Journal of Pharmacy and Pharmacology (1986), 38(11), 829-33
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB Previous studies having shown that chloroquine [54-05-7] and hydroxychloroquine [118-42-3] could reduce interleukin 1 (IL-1)-induced cartilage degrdn. in-vitro, the effects of a range of antimalarial drugs on the cartilage proteoglycan degrading actions of porcine leukocyte .alpha.-interleukin 1 were examd. using the std. bovine nasal cartilage culture system. The anti-IL-1 effects in this system were specific to several aminoquinoline and aminoacridine analogs having a side chain with a tertiary amino group similar to that of chloroquine. Aminoquinoline compds. devoid of this side chain and the tertiary amino, as well as pyrimidines or biguanides with antimalarial activity were without effect. Mefloquine [53230-10-7], the most potent of the compds. active against porcine .alpha.-IL-1, was only equipotent with chloroquine and its hydroxy analog against **human** recombinant .alpha.-IL-1. This suggests that there may be subtle differences in the receptors for these drugs and interleukins in bovine cartilage. The results provide further evidence for the specificity and utility of antimalarial drugs in the treatment of chronic inflammatory conditions, esp. in relation to actions on IL-1.

L13 ANSWER 24 OF 26 CAPLUS
AN 1986:454142 CAPLUS
DN 105:54142
TI Hypoglycemia and antimalarial drugs: **quinidine** and release of insulin
AU Phillips, R. E.; Looareesuwan, Sornchai; White, N. J.; Chanthavanich, Pornthep; Karbwang, Juntra; Supanaranond, Wichai; Turner, R. C.; Warrell,

D. A.
CS Fac. Trop. Med., Mahidol Univ., Bangkok, 10400, Thailand
SO British Medical Journal (1986), 292(6531), 1319-21
CODEN: BMJOAE; ISSN: 0007-1447
DT Journal
LA English
AB Life threatening hypoglycemia has been closely assocd. with the use of **quinidine** gluconate [7054-25-3] but the effect of **quinidine** and the synthetic **antimalarials** on the homeostasis of glucose has not been investigated. In volunteers given a fixed dose of 500 mg base and patients with malaria given a **quinidine** loading dose (15 mg base/kg) mean plasma insulin [9004-10-8] concns. rose from 6.1 mU/L to 10.9 mU/L and 10.4 mU/L to 18.5 mU/L, resp. Plasma glucose concns. fell from 4.5 mmol/L to 4.0 mmol/L in volunteers and from 5.7 mmol/L to 4.8 mmol/L in patients. One of two patients with cerebral malaria and acute renal failure became profoundly hypoglycemic. Hypoglycemia may occur in any severely ill fasting patient given parenteral **quinidine**. The other **antimalarials** tested, chloroquine [54-05-7], amodiaquine [86-42-0], mefloquine [53230-10-7], and halofantrine [69756-53-2] did not stimulate the release of insulin, an important advantage that should be taken into account when treatment is chosen for Plasmodium falciparum malaria.

L13 ANSWER 25 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1972:428668 CAPLUS
DN 77:28668
TI Aspects of **human** pharmacogenetics.
AU Rico, J. M. Giao T.
CS Port.
SO Actualidades Biologicas (Lisbon) (1971), 43, 195-242
CODEN: ABOLAA; ISSN: 0365-0804
DT Journal; General Review
LA Portuguese
AB A review with 55 refs. The role of genetics on the responses of **humans** to drugs is discussed in relation to hemolytic reactions to **antimalarials**, sulfamides, sulfones, analgesics, and **quinidine** in enzyme deficiencies. The genetics of enzyme deficiencies leading to defective Hb synthesis are also described.

L13 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2003 ACS
AN 1950:1100 CAPLUS
DN 44:1100
OREF 44:223e-h
TI A study of **antimalarials** and antimalarial activity in the **human** malarials
AU Shannon, James A.
SO Harvey Lectures Ser. (1946), Volume Date 1945-1946, 41, 43-89
DT Journal
LA Unavailable
AB Malaria was induced in susceptible patients by the intravenous inoculation of blood contg. 500, 000 parasites of either the McCoy strain or the Chesson strain of P. vivax. Administration of the **antimalarials** was begun after 4 to 5 days of fever and continued in a manner calcd. to maintain a stable plasma drug concn. for a 4- to 6-day period. The antimalarial activity of quinine was found to be an expression of its plasma concn.; the concn. necessary to interrupt the asexual cycle of the McCoy strain was 5 mg./l. for 4 days and of the Chesson strain 6 mg./l.

for 6 days. The action of the drug was suppressive in type and wholly limited to the erythrocyte forms of the parasites and had no effect on the primary tissue phase or the persisting tissue phase of the mosquito-induced disease. When maintained for 4 days, the effective plasma levels for **quinidine**, cinchonidine, cinchonine, and quinacrine were 10 mg., 3.0 mg., 0.1 mg. and 26.0 .gamma./l., resp., for the McCoy strain. Avian malaria responds differently to drugs than does vivax malaria.

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L16 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2003:90670 CAPLUS
DN 138:180259
TI Effect of primaquine standard dose (15 mg/day for 14 days) in the treatment of vivax malaria patients in Thailand
AU Buchachart, K.; Krudsood, S.; Singhasivanon, P.; Treeprasertsuk, S.; Phophak, N.; Srivilairit, S.; Chalermrut, K.; Rattanapong, Y.; Supeeranuntha, L.; Wilairatana, P.; Brittenham, G.; Looareesuwan, S.
CS Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
SO Southeast Asian Journal of Tropical Medicine and Public Health (2001), 32(4), 720-726
CODEN: SJTMAK; ISSN: 0125-1562
PB SEAMEO-TROPMED Network
DT Journal
LA English
AB Primaquine (8-aminoquinoline), the only effective drug to prevent relapses of the persistent liver forms of Plasmodium vivax and Plasmodium ovale, can induce hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The severity varies considerably among affected individuals. Three hundred and sixty-four Plasmodium vivax cases (342 G6PD-normal and 22 G6PD-deficient) were given a 3-day course of chloroquine (total dose 1,500 mg) followed by primaquine 15 mg a day for 14 days and completed a 28-day follow-up. All G6PD-deficient patients were male; there were no relapses or serious adverse events during the study. Although a significant decrease in hematocrit levels and an increase in the percent redn. of hematocrit levels were obsd. on day 7 (34.9 .+-. 5.0 vs. 26.7 .+-. 5.4; (-1.2) .+-. 14.4 vs. (-24.5) .+-. 13.9 resp.) and on day 14 (35.7 .+-. 4.3 vs. 30.9 .+-. 3.1; 1.6 .+-. 17.8 vs. (-11.0) .+-. 19.3 resp.) blood transfusion was not required. Daily doses of 15 mg of primaquine for 14 days following a full course of chloroquine when prescribed to Thai G6PD deficient patients where Mahidol variant is predominant, are relatively safe.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2001:289703 CAPLUS
DN 135:204876
TI Rapid therapeutic response onset of a new pharmaceutical form of **chloroquine phosphate** 300 mg: effervescent tablets
AU Yanze, Maximun Frederic; Duru, Christian; Jacob, Maurice; Bastide, Jean Marie; Lankeuh, Marguerite
CS Laboratoire de Galenique, Pharmacotechnie et Biopharmacie, Universite de Montpellier I, Fr.

SO Tropical Medicine & International Health (2001), 6(3), 196-201
CODEN: TMIHFL; ISSN: 1360-2276
PB Blackwell Science Ltd.
DT Journal
LA English
AB Objective: To compare the efficiency, safety, and taste of two pharmaceutical forms of **chloroquine phosphate** 300 mg: effervescent tablets against uncoated tablets. Method: An open randomized study with 60 adults who suffered from acute uncomplicated Plasmodium falciparum malaria in three health centers in Nkongsamba health district, Cameroon. Results: Mean times to fever clearance, symptoms clearance and asexual parasites clearance were longer in the uncoated tablets group: 36 h (range 24-48 h, SD = 16.8) vs. 60 h (range 24-96 h, SD = 31.2, P = 0.001) for fever clearance, 36 h (24-48 h, SD = 16.8) vs. 48 h (24-72, SD = 24, P = 0.001) for symptoms clearance and 48 h (24-72, SD = 1) vs. 72 h (48-96, SD = 24, P = 0.001)for parasitemia clearance. Uncoated tablets took significantly longer to achieve 50% redn. of the initial asexual parasite d.: (mean/SD) 19.2 h/7 vs. 52.8 h/16.8, P < 0.00001. The adverse effects in the two groups were similar, P > 0.05. The cure rate at day 7 in the two groups was similar, P > 0.05. There was no chloroquine resistance in the effervescent tablets group but one RI and one RII resistance in the uncoated tablets group. The taste of the two pharmaceutical forms was significantly different, P < 0.00001. Effervescent tablets tasted sweet (score = 7.93), whereas uncoated tablets were bitter (score = 2.07). Conclusion: Effervescent tablets of **chloroquine phosphate** 300 mg work faster than uncoated tablets and because of their safe use and sweet taste achieve good therapeutic compliance.
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 6 CAPLUS
AN 2001:120883 CAPLUS
DN 135:146814
TI A molecular marker for chloroquine-resistant falciparum malaria
AU Djimde, Abdoulaye; Doumbo, Ogobara K.; Cortese, Joseph F.; Kayentao, Kassoum; Doumbo, Safi; Diourte, Yacouba; Dicko, Alassane; Su, Xin-Zhuan; Nomura, Takashi; Fidock, David A.; Wellems, Thomas E.; Plowe, Christopher V.
CS Malaria Section, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SO New England Journal of Medicine (2001), 344(4), 257-263
CODEN: NEJMAG; ISSN: 0028-4793
PB Massachusetts Medical Society
DT Journal
LA English
AB Chloroquine-resistant Plasmodium falciparum malaria is a major health problem, particularly in sub-Saharan Africa. Chloroquine resistance has been assocd. in vitro with point mutations in two genes, pfcrt and pfmdr 1, which encode the P. falciparum digestive-vacuole transmembrane proteins PfCRT and Pgh1, resp. To assess the value of these mutations as markers for clin. chloroquine resistance, we measured the assocn. between the mutations and the response to chloroquine treatment in patients with uncomplicated falciparum malaria in Mali. The frequencies of the mutations in patients before and after treatment were compared for evidence of selection of resistance factors as a result of exposure to chloroquine. The pfcrt mutation resulting in the substitution of

threonine (T76) for lysine at position 76 was present in all 60 samples from patients with chloroquine-resistant infections (those that persisted or recurred after treatment), as compared with a base-line prevalence of 41 percent in samples obtained before treatment from 116 randomly selected patients (P<0.001), indicating abs. selection for this mutation. The pfmdr 1 mutation resulting in the substitution of tyrosine (Y86) for asparagine at position 86 was also selected for, since it was present in 48 of 56 post-treatment samples from patients with chloroquine-resistant infections (86 percent), as compared with a base-line prevalence of 50 percent in 115 samples obtained before treatment (P<0.001). The presence of pfcrt T76 was more strongly assocd. with the development of chloroquine resistance (odds ratio, 18.8; 95 percent confidence interval, 6.5 to 58.3) than was the presence of pfmdr 1 Y86 (odds ratio, 3.2; 95 percent confidence interval, 1.5 to 6.8) or the presence of both mutations (odds ratio, 9.8; 95 percent confidence interval, 4.4 to 22.1). This study shows an assocn. between the pfcrt T76 mutation in P. falciparum and the development of chloroquine resistance during the treatment of malaria. This mutation can be used as a marker in surveillance for chloroquine-resistant falciparum malaria.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1998:147346 CAPLUS
DN 128:213381
TI Compositions and methods for treating infections using analogs of indolicidin
IN Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
PA Micrologix Biotech, Inc., Can.; Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9807745	A2	19980226	WO 1997-US14779	19970821
	WO 9807745	A3	19980709		

W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
	AU 9743279	A1	19980306	AU 1997-43279	19970821
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				WO 1997-US14779W	19970821
	EP 925308	A2	19990630	EP 1997-941352	19970821
	EP 925308	B1	20020605		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

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     EP 1174439        A3   20030326
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                                         EP 1997-941352 A319970821
     AT 218579         E    20020615     AT 1997-941352   19970821
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                                         US 1997-34949P P 19970113
                                         WO 1997-US14779W 19970821
     ES 2178000        T3   20021216     ES 1997-941352   19970821
                                         US 1996-24754P P 19960821
                                         US 1997-34949P P 19970113
PATENT FAMILY INFORMATION:
FAN  1998:621235
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PI   WO 9840401        A2   19980917     WO 1998-CA190    19980310
     WO 9840401        A3   19981217
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             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
             UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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                                         US 1997-40649P P 19970310
                                         US 1997-915314 A 19970820
                                         US 1997-60099P P 19970926
     US 6180604        B1   20010130     US 1997-915314   19970820
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                                         US 1997-34949P P 19970113
     AU 9866047        A1   19980929     AU 1998-66047    19980310
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                                         US 1997-915314 A 19970820
                                         US 1997-60099P P 19970926
                                         US 1998-30619  A 19980225
                                         WO 1998-CA190  W 19980310
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                                         US 1997-915314 A 19970820
                                         US 1997-60099P P 19970926
                                         US 1998-30619  A 19980225
                                         WO 1998-CA190  W 19980310
     JP 2002544759     T2   20021224     JP 1998-538997   19980310
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                                                  US 1997-40649P P 19970310
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FAN  2002:221202
     PATENT NO.        KIND  DATE             APPLICATION NO.  DATE
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PI   US 2002035061      A1   20020321         US 1998-30619    19980225
     US 6503881         B2   20030107
                                              US 1996-24754P P 19960821
                                              US 1997-34949P P 19970113
                                              US 1997-40649P P 19970310
                                              US 1997-915314 A219970820
                                              US 1997-60099P P 19970926
     US 6180604         B1   20010130         US 1997-915314   19970820
                                              US 1996-24754P P 19960821
                                              US 1997-34949P P 19970113
     EP 1174439         A2   20020123         EP 2001-119148   19970821
     EP 1174439         A3   20030326
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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                                              US 1996-24754P P 19960821
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             IE, FI
                                              US 1997-40649P P 19970310
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                                              US 1997-60099P P 19970926
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                                              WO 1998-CA190  W 19980310
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                                              US 1997-915314 A 19970820
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                                              US 1998-30619  A 19980225
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     US 6538106         B1   20030325         US 2000-667486   20000922
                                              US 1996-24754P P 19960821
                                              US 1997-34949P P 19970113
                                              US 1997-915314 A119970820
```

OS MARPAT 128:213381

AB Compns. and methods for treating infections, esp. bacterial infections, are provided. Indolicidin peptide analogs contg. at least two basic amino acids are prepd. The analogs are administered as modified peptides, preferably contg. photo-oxidized solubilizer.

L16 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1995:305779 CAPLUS

DN 122:72009
TI Desipramine in the treatment of drug-resistant malarial infections
IN Mccann, Peter P.; Sjoerdsma, Albert; Bitonti, Alan J.
PA Merrell Dow Pharmaceuticals Inc., USA
SO U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 925,703, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5373005	A	19941213	US 1993-26950	19930305
				US 1988-183858	19880420
				US 1988-243524	19880912
				US 1989-333156	19890404
				US 1990-590437	19900926
				US 1991-725940	19910627
				US 1992-925703	19920804
	ZA 8902724	A	19891227	ZA 1989-2724	19890413
				US 1988-183858	19880420

PATENT FAMILY INFORMATION:
FAN 1990:210970

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 338532	A2	19891025	EP 1989-107027	19890419
	EP 338532	A3	19910130		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
				US 1988-183858	19880420
				US 1988-243524	19880912
	ZA 8902724	A	19891227	ZA 1989-2724	19890413
				US 1988-183858	19880420
	AU 8933023	A1	19891026	AU 1989-33023	19890414
	AU 625071	B2	19920702		
				US 1988-183858	19880420
				US 1988-243524	19880912
	JP 01311026	A2	19891215	JP 1989-98642	19890418
				US 1988-183858	19880420
				US 1988-243524	19880912
	DK 8901901	A	19891021	DK 1989-1901	19890419
				US 1988-183858	19880420
				US 1988-243524	19880912

AB Drug-resistant malarial infection in **humans** can be effectively treated with std. antimalarial agents if administered in conjunction with desipramine. The synergism of chloroquine with desipramine against chloroquine-resistant Plasmodium falciparum is shown. A tablet formulation including **chloroquine phosphate** and desipramine-HCl is presented.

L16 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1975:558421 CAPLUS
DN 83:158421
TI Prevention of drug resistance in rodent malaria by the use of drug mixtures
AU Peters, W.
CS Dep. Parasitol., Liverpool Sch. Trop. Med., Liverpool, UK
SO Bulletin of the World Health Organization (1974), 51(4), 379-84
CODEN: BWHOA6; ISSN: 0366-4996

DT Journal
LA English
AB Development of resistance to **chloroquine phosphate** [50-63-5] in rodent malaria was inhibited by administration of this compd. together with a potentiating mixt. of pyrimethamine [58-14-0] and sulfadoxine [2447-57-6] to mice infected with Plasmodium berghei. This procedure did not prevent the development of resistance to the last 2 compds. The use of drug mixts. apparently should be explored as a means of protecting chloroquine or new blood schizontocides intended for mass chemotherapy against **human** malaria. No general rule, however, can be laid down without testing specific drug mixts. in long-term expts. in a suitable model such as rodent malaria.

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COST IN U.S. DOLLARS                             SINCE FILE      TOTAL
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NETWORK CHARGES                                        1.44       1.56
SEARCH CHARGES                                        24.60     172.35
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3: Ronn AM, et al. [A renewed effort against mal...[PMID:12701308] Links

4: Wilson JF. Advancing the war on malaria....[PMID:12693913] Related Articles, Links

5: Gilani JM, et al. The global and local impact o...[PMID:12693189] Related Articles, Links

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1: Haivas I. Related Articles, Links

Roll Back Malaria campaign still has a long way to go.
BMJ. 2003 May 3;326(7396):951. No abstract available.
PMID: 12727754 [PubMed - indexed for MEDLINE]

2: Andreopoulos S. Related Articles, Links

Developing drugs for parasitic diseases.
Science. 2003 Apr 18;300(5618):430-1. No abstract available.
PMID: 12702858 [PubMed - indexed for MEDLINE]

3: Ronn AM, Vestergaard LS, Bygbjerg IC. Links

[A renewed effort against malaria. The Danish Society of Tropical Medicine&International Health]
Ugeskr Laeger. 2003 Mar 17;165(12):1258. Danish. No abstract available.
PMID: 12701308 [PubMed - indexed for MEDLINE]

4: Wilson JF. Related Articles, Links

Advancing the war on malaria.
Ann Intern Med. 2003 Apr 15;138(8):693-6. No abstract available.
PMID: 12693913 [PubMed - indexed for MEDLINE]

5: Gilani JM, Khan OA. Related Articles, Links

The global and local impact of malaria: a case report from Delaware, advances in treatment, and recommendations for travelers.
Del Med J. 2003 Feb;75(2):57-65. No abstract available.
PMID: 12693189 [PubMed - indexed for MEDLINE]

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FX - Means Fa[x] us

1: Antimicrob Agents Chemother 1999 Mar;43(3):598-602 Relat

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8-Aminoquinolines active against blood stage Plasmodium f vitro inhibit hematin polymerization.

Vennerstrom JL, Nuzum EO, Miller RE, Dorn A, Gerena L, Dande P Ridley RG, Milhous WK.

Department of Pharmaceutical Sciences, College of Pharmacy, University Medical Center, Omaha 68198-6025. jvenners@mail.unmc.edu

From the Walter Reed Army Institute of Research (WRAIR) inventory, th 8-aminoquinoline analogs of primaquine were selected for screening again seven Plasmodium falciparum clones and isolates. Six of the 13 8-aminoqu average 50% inhibitory concentrations between 50 and 100 nM against the clones and were thus an order of magnitude more potent than primaquine. excluding chloroquine-resistant clones and isolates, these 8-aminoquinoli order of magnitude less potent than chloroquine. None of the 8-aminoquin resistant with either chloroquine or mefloquine. In contrast to the inactive prototype, 8 of the 13 8-aminoquinolines inhibited hematin polymerization than did chloroquine. Although alkoxy or aryloxy substituents at position endowed these 13 8-aminoquinolines with impressive schizontocidal activi specificity of inhibition of both parasite growth and hematin polymerizatio

PMID: 10049273 [PubMed - indexed for MEDLINE]

2: Am J Trop Med Hyg 1998 May;58(5):645-9 Relat

First-time-in-humans safety and pharmacokinetics of WR 2 antimalarial.

Brueckner RP, Lasseter KC, Lin ET, Schuster BG.

Division of Experimental Therapeutics, Walter Reed Army Institute of Re:
Washington, District of Columbia 20307-5100, USA.

WR 238605 is an 8-aminoquinoline drug currently under development for
treatment of malaria. Preclinical studies have demonstrated that it has grea
less toxicity compared with primaquine. In this first-time-in-human randon
double-blind, placebo-controlled study designed to evaluate the safety, tol
pharmacokinetics, WR 238605 was administered to 48 men in single oral
from four to 600 mg (base). It was well tolerated, with gastrointestinal dis
possible side effects. Linear kinetics were demonstrated at these doses. Wl
long absorption phase and is slowly metabolized, with a tmax of 12 hr and
half-life of 14 days. These safety, efficacy and pharmacokinetic properties
an excellent candidate for further testing as a prophylactic, radical curative
eradication drug.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 9598455 [PubMed - indexed for MEDLINE]

(3) 5: Bull World Health Organ 1995;73(5):565-71 Relat

Status of antimalarial drugs under development.

Olliaro PL, Trigg PI.

Steering Committee on Drugs for Malaria, UNDP/World Bank/WHO Spe
for Research and Training in Tropical Diseases, World Health Organizatio
Switzerland.

Despite the urgent need of a new antimalarial drugs, particularly those aga
multiresistant falciparum malaria, only a limited number of drugs are now :
stage of preclinical or clinical development. They include artemisinin deriv
pyronaridine and benflumetol (all originally developed in China), as well a:
combinations, the hydroxynaphoquinone atovaquone which has a novel m
and a new 8-aminoquinoline which appears more active and less toxic thar
Some of these drugs may become available in the next few years. It is ther

to find mechanisms to ensure that they are made available at an affordable
populations that really need them.

Publication Types:
- Review
- Review, Tutorial

PMID: 8846482 [PubMed - indexed for MEDLINE]

3: Curr Infect Dis Rep 2001 Feb;3(1):68-76 Related Articles, Links

CURRENT reports

Recent Advances in the Prophylaxis and Treatment of Malaria.

Labbe AC, Loutfy MR, Kain KC.

Department of Medicine, Tropical Disease Unit, University Health Network, University of Toronto, 200 Elizabeth Street, EN G 224, Toronto, ON, Canada, M5G 2C4. kevin.kain@uhn.on.ca.

Increases in international travel and escalating drug resistance are putting put a growing number of travelers at risk of contracting malaria. Resistance to chloroquine and proguanil and real and perceived intolerance to standard agents, such as mefloquine, has highlighted the need for new antimalarials to prevent and treat malaria. Promising new agents to prevent malaria include the combination of atovaquone and proguanil, primaquine, and a related 8-aminoquinoline, tafenoquine. These agents are active against the liver stage of the malaria parasite, and therefore can be discontinued shortly after the traveler leaves the malaria-endemic area; this offers a clear advantage, in terms of adherence to a treatment regimen. For treatment of multidrug-resistant Plasmodium falciparum malaria, the combination of artemisinin derivatives plus mefloquine, or atovaquone plus proguanil, are the most active drug regimens.

PMID: 11177733 [PubMed - as supplied by publisher]

L9 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1998:271708 CAPLUS
DN 129:36145
TI Prophylaxis of Plasmodium falciparum infection in a **human** challenge model with WR 238605, a new **8-aminoquinoline** antimalarial
AU Brueckner, Ralf P.; Coster, Trinka; Wesche, David L.; Shmuklarsky, Moshe; Schuster, Brian G.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC, 20307-5100, USA
SO Antimicrobial Agents and Chemotherapy (1998), 42(5), 1293-1294
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
AB The prophylactic efficacy of WR 238605, a primaquine analog, was studied with a **human** Plasmodium falciparum challenge model. A single oral dose of 600 mg, administered 1 day prior to challenge, successfully protected three of four subjects. The fourth subject developed mild, oligosymptomatic malaria on day 31, with drug concns. one-half of those in the protected individuals. WR 238605 appears to be a promising prophylactic drug for P. falciparum malaria.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1995:966060 CAPLUS
DN 124:20887
TI Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war
AU Greenwood, David
CS Wellcome Inst. History Med., London, NW1 2BE, UK
SO Journal of Antimicrobial Chemotherapy (1995), 36(5), 857-72
CODEN: JACHDX; ISSN: 0305-7453
PB Saunders
DT Journal; General Review
LA English
AB A review with 52 refs. Malaria has had an enormous impact on **human** history, not least in times of war. The disease has been treatable by a natural remedy, quinine, since the 17th century, but the prodn. of synthetic antimalarial agents was first achieved in Germany in the wake of the Great War of 1914-1918, in which malaria had caused immense problems. In the 1920s research workers in the Bayer labs. of the IG Farbenindustrie consortium developed the **8-aminoquinoline** plasmoquine (the forerunner of primaquine). They went on to develop the acridine dye, atebrin (mepacrine) and the 4-aminoquinolines, Resochin (developed at the end of the Second World War in America as chloroquine) and Sontochin. British attempts to match the advances achieved by the Germans were at first unproductive, partly because collaboration between academic and industrial organizations in the UK was beset by concerns over patent rights. However, with the outbreak of World War II, when supplies of **antimalarials** were scarce, ICI succeeded in the large-scale prodn. of mepacrine (essential to prosecution of the war, particularly in the Far East) and also initiated a program of collaborative research that eventually led to the discovery of proguanil (Paludrine); this, in its turn led to the diaminopyrimidine, pyrimethamine. A massive cooperative screening program in the USA during World War II eventually bore fruit in the realization of the therapeutic potential of chloroquine, and in the later development of amodiaquine and primaquine. Some of this work also influenced the subsequent discovery of mefloquine and halofantrine at the Walter Reed Army Institute of Research.

Nice

L16 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS

AN	1998:147346 CAPLUS
DN	128:213381
TI	Compositions and methods for treating infections using analogs of indolicidin
IN	Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
PA	Micrologix Biotech, Inc., Can.; Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
SO	PCT Int. Appl., 130 pp. CODEN: PIXXD2
DT	Patent
LA	English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9807745	A2	19980226	WO 1997-US14779	19970821
	WO 9807745	A3	19980709		

W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
	AU 9743279	A1	19980306	AU 1997-43279	19970821
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				WO 1997-US14779W	19970821
	EP 925308	A2	19990630	EP 1997-941352	19970821
	EP 925308	B1	20020605		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

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          IE, FI
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
                                            WO 1997-US14779W 19970821
     JP 2001500477     T2   20010116        JP 1998-510994    19970821
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
                                            WO 1997-US14779W 19970821
     EP 1174439        A2   20020123        EP 2001-119148    19970821
     EP 1174439        A3   20030326
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, FI
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
                                            EP 1997-941352 A319970821
     AT 218579         E    20020615        AT 1997-941352    19970821
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
                                            WO 1997-US14779W 19970821
     ES 2178000        T3   20021216        ES 1997-941352    19970821
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
PATENT FAMILY INFORMATION:
FAN  1998:621235
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 9840401        A2   19980917        WO 1998-CA190    19980310
     WO 9840401        A3   19981217
        W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
            DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
            LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
            UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
            FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
            GA, GN, ML, MR, NE, SN, TD, TG
                                            US 1997-40649P P 19970310
                                            US 1997-915314 A 19970820
                                            US 1997-60099P P 19970926
     US 6180604        B1   20010130        US 1997-915314    19970820
                                            US 1996-24754P P 19960821
                                            US 1997-34949P P 19970113
     AU 9866047        A1   19980929        AU 1998-66047     19980310
                                            US 1997-40649P P 19970310
                                            US 1997-915314 A 19970820
                                            US 1997-60099P P 19970926
                                            US 1998-30619  A 19980225
                                            WO 1998-CA190  W 19980310
     EP 966481         A2   19991229        EP 1998-907779    19980310
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, FI
                                            US 1997-40649P P 19970310
                                            US 1997-915314 A 19970820
                                            US 1997-60099P P 19970926
                                            US 1998-30619  A 19980225
                                            WO 1998-CA190  W 19980310
     JP 2002544759     T2   20021224        JP 1998-538997    19980310
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				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310

FAN 2002:221202

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002035061	A1	20020321	US 1998-30619	19980225
	US 6503881	B2	20030107		
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				US 1997-40649P P	19970310
				US 1997-915314 A2	19970820
				US 1997-60099P P	19970926
	US 6180604	B1	20010130	US 1997-915314	19970820
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
	EP 1174439	A2	20020123	EP 2001-119148	19970821
	EP 1174439	A3	20030326		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				EP 1997-941352 A3	19970821
	AU 9866047	A1	19980929	AU 1998-66047	19980310
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	EP 966481	A2	19991229	EP 1998-907779	19980310
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	JP 2002544759	T2	20021224	JP 1998-538997	19980310
				US 1997-40649P P	19970310
				US 1997-915314 A	19970820
				US 1997-60099P P	19970926
				US 1998-30619 A	19980225
				WO 1998-CA190 W	19980310
	US 6538106	B1	20030325	US 2000-667486	20000922
				US 1996-24754P P	19960821
				US 1997-34949P P	19970113
				US 1997-915314 A1	19970820

OS MARPAT 128:213381

AB Compns. and methods for treating infections, esp. bacterial infections, are provided. Indolicidin peptide analogs contg. at least two basic amino acids are prepd. The analogs are administered as modified peptides, preferably contg. photo-oxidized solubilizer.

L16 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS

AN 1995:305779 CAPLUS

DN 122:72009
TI Desipramine in the treatment of drug-resistant malarial infections
IN Mccann, Peter P.; Sjoerdsma, Albert; Bitonti, Alan J.
PA Merrell Dow Pharmaceuticals Inc., USA
SO U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 925,703, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5373005	A	19941213	US 1993-26950	19930305
				US 1988-183858	19880420
				US 1988-243524	19880912
				US 1989-333156	19890404
				US 1990-590437	19900926
				US 1991-725940	19910627
				US 1992-925703	19920804
	ZA 8902724	A	19891227	ZA 1989-2724	19890413
				US 1988-183858	19880420

PATENT FAMILY INFORMATION:
FAN 1990:210970

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 338532	A2	19891025	EP 1989-107027	19890419
	EP 338532	A3	19910130		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
				US 1988-183858	19880420
				US 1988-243524	19880912
	ZA 8902724	A	19891227	ZA 1989-2724	19890413
				US 1988-183858	19880420
	AU 8933023	A1	19891026	AU 1989-33023	19890414
	AU 625071	B2	19920702		
				US 1988-183858	19880420
				US 1988-243524	19880912
	JP 01311026	A2	19891215	JP 1989-98642	19890418
				US 1988-183858	19880420
				US 1988-243524	19880912
	DK 8901901	A	19891021	DK 1989-1901	19890419
				US 1988-183858	19880420
				US 1988-243524	19880912

AB Drug-resistant malarial infection in **humans** can be effectively treated with std. antimalarial agents if administered in conjunction with desipramine. The synergism of chloroquine with desipramine against chloroquine-resistant Plasmodium falciparum is shown. A tablet formulation including **chloroquine phosphate** and desipramine-HCl is presented.

L16 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1975:558421 CAPLUS
DN 83:158421
TI Prevention of drug resistance in rodent malaria by the use of drug mixtures
AU Peters, W.
CS Dep. Parasitol., Liverpool Sch. Trop. Med., Liverpool, UK
SO Bulletin of the World Health Organization (1974), 51(4), 379-84
CODEN: BWHOA6; ISSN: 0366-4996

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tance to **chloroquine phosphate**
malaria was inhibited by administration of this compd.
ntiating mixt. of pyrimethamine [58-14-0] and
-6] to mice infected with Plasmodium berghei. This
event the development of resistance to the last 2
drug mixts. apparently should be explored as a means
quine or new blood schizontocides intended for mass
human malaria. No general rule, however,
hout testing specific drug mixts. in long-term expts.
such as rodent malaria.

L8 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1956:4972 CAPLUS
DN 50:4972
OREF 50:1092d-h
TI Aromatic aminoalkylamines
IN Cusic, John W.
PA G. D. Searle & Co.
DT Patent
LA Unavailable
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2687414		19540824	US	

AB Condensing an aminoalkyl ester and a secondary aromatic amine in the presence of caustic alkali gave tertiary aromatic amines. Thus, Ph2NH 334, Et2NHCH2CH2Cl 540, and powd. NaOH 160 were mixed thoroughly and heated to about 100.degree., (after 2 hrs. the mixt. became solid), more Et2NHCH2CH2Cl was added to aid agitation, the mixt. heated 13 hrs. at 100.degree. extd. with Et2O, the Et2O soln. washed with H2O, dried and evapd., and the residue distd. to give Ph2NCH2CH2NEt2, b7 166-8.degree.; HCl salt, m. 167-8.degree. (from MeEtCO). Similarly prepd. was Ph2NCH2CH2NMe2.HCl, m. 246-7.degree., and the following 9-R-substituted carbazoles (R given): Et2NCH2CH2, b6 197-200.degree. [HCl salt, m. 124-5.degree.; methiodide, m. 188-90.degree.; tetrahydro deriv. b5 184-5.degree. (HCl salt, m. 138-40.degree.)]; Me2NCH2CH2, tetrahydro deriv. HCl salt, m. 243-4.degree.; MeCH(NMe2)CH2, b0.3 157.degree. (HCl salt, m. about 235.degree.; tetrahydro compd., b0.15 138-45.degree.); .beta.piperidinoethyl, tetrahydro deriv., b5 190-3.degree.; .beta.-morpholinoethyl, tetrahydro deriv., b4 184-8.degree.; EtCH(NMe2)CH2, tetrahydro deriv., b0.1 147-52.degree.; Me2NCH2CH2CH2, tetrahydro deriv., b2 172-7.degree.; and Bu2NCH2CH2, tetrahydro deriv. The following 10-R-substituted phenothiazines were prepd. (R given): Et2NCH2CH2, b6 208-12.degree. (HCl salt, m. 180-3.degree.); Me2NCH2CH2CH2, b3 203-5.degree.; Me2NCH2CH2, 5-oxide, m. 132-3.degree.; MeCH(NHMe2)CH2, HCl salt, m. 205-7.degree. (citrate, m. 157-8.degree.); .beta.-piperidinoethyl, b3-4 225-35.degree. (HCl salt, m. 172-4.degree.); .beta.-pyrrolidinoethyl, b2 222-6.degree. (HCl salt, m. 196-7.degree.; EtCH(NMe2)CH2, b4.5 200-10.degree. (citrate, m. 142-5.degree.); Me2NCH2CH2, m. 42.degree.; .beta.-pyrrolidinopropyl, b1 212-6.degree.; .beta.-pyrrolidinopropyl, b1 210-13.degree.; MeCH(NMe2)CH2; BuNHCH2CH2; Me2C(NMe2)CH2, b1 175-80.degree.; .beta.-morpholinoethyl, b3-4 225-35.degree. (HCl, m. 172-4.degree.). Similarly prepd. were Ph2NCH2CH2NMe2.HCl, m. 246-7.degree.; Ph2N(CH2)3NEt2, b5 161-4.degree.; and Ph2NCH2CHMeNMe2.HCl, m. 161-2.degree.; and the following 10-R-substituted acridans (R given): Me2NCH2CH2, b3-4 180-90.degree. (HCl salt, m. 227-9.degree.), .beta.-piperidinoethyl, and Et2NCH2CH2, b4 196-203.degree.. 10-(.gamma.-Dimethylamino-.beta.,.beta.-dimethyl)propylphenothiazine, 10-(2,6-dimethylpiperidinoethyl)-phenothiazine, b1 225.degree., 10-(.beta.-dimethylamino)ethylphenoxazine-HCl, m. 241.degree., and N-(.beta.-dimethylaminoethyl)cyclohexylaniline, b4 156-60.degree., were also prepd. These compds. are valuable in the manufacture of medicinal agents, as histamine antagonists and antispasmodic agents. Cf. C.A. 45, 7152b; 47, 1194a; 48, 1444f.
IT **3733-37-7**, Phenothiazine, 10-[3-(1-pyrrolidinyl)propyl]-
(prepn. of)
RN 3733-37-7 CAPLUS
CN Phenothiazine, 10-[3-(1-pyrrolidinyl)propyl]- (6CI, 7CI, 8CI) (CA INDEX NAME)